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HERITABLE DISORDERS OF CONNECTIVE TISSUE

III. The Marfan Syndrome

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HISTORICAL SURVEY

IN 1896[101] the gross skeletal manifestations of the syndrome which bears his name were described by Marfan,* who called the condition *dolichostenomelia* (long, thin extremities). The condition was renamed arachnodactyly by Achard in 1902.[3] Salle[136] in 1912 reported necropsy observations in the case of a 2½-month-old infant who died with cardiac symptoms and showed generalized dilatation of the heart and patent foramen ovale. Boerger[24] first clearly related ectopia lentis to the other manifestations. As is usually the case, vague references to cases of what was certainly this syndrome can be found in medical reports antedating the definitive descriptions. For instance, Williams,[183] an opthalmologist in Cincinnati, in 1876 described ectopia lentis in a brother and sister who were exceptionally tall and had been loose-jointed from birth.

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*Antoine Bernard-Jean Marfan (1858-1942), Parisian professor of pediatrics, did much to establish pediatrics as a specialty in France and elsewhere. He was the author of several widely read textbooks and monographs on pediatric topics and editor of *Le Nourrison* for a great many years. In addition to the syndrome under discussion here, his name is often attached to Marfan's law (that immunity to pulmonary phthisis is conferred by the healing of a local tuberculous lesion) and Marfan's subxiphoid method for aspirating fluid from the pericardial sac. (For other biographic details, see references 6, 7, 8, 74; for portrait, see reference 8.)

Weve of Utrecht,[177] publishing in 1931, first clearly demonstrated the heritable nature of the syndrome and its transmission as a dominant trait. Furthermore he conceived of this syndrome as a disorder of mesenchymal tissues and accordingly designated it *dystrophia mesodermalis congenita, typus Marfanis.*

The major cardiovascular complications, namely, aortic dilatation and dissecting aneurysm, were first clearly described in 1943 by Baer, Taussig, and Oppenheimer[11] and by Etter and Glover,[42] respectively. Again, although earlier reports of the aortic complications can be discovered (e.g., reference 29), these latter authors first drew attention to them and opened the way for clearer recognition of the internal medical implications of this syndrome in adults.

"Marfan's syndrome," or better, "the Marfan syndrome," is, in my opinion, the preferred designation until such time as the basic defect is known and an accurate name based thereon can be devised. Arachnodactyly is, on the one hand, not striking in some patients, and, on the other hand, occurs with other developmental disorders, both acquired and genetic.

Probably at least 350 cases of the Marfan syndrome have been reported in the literature. By intensive searches of multiple sources, I was able in the last three years to collect 50 kinships in which at least one bona fide affected person has occurred. Nineteen of these definitely affected families are represented in the accompanying illustrative material and data from seven other definitely affected families have been presented elsewhere.[92] The total number of affected persons in these pedigrees is in excess of 100. In this study, the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital was the largest single source of propositi. However, other sources included pediatricians, orthopedists, endocrinologists, and cardiologists. The Medical Examiner's Office was another fruitful source; tracing the relatives of young individuals dying of dissecting aneurysm of the aorta revealed several affected kinships.

VOL. 2 1955

CLINICAL MANIFESTATIONS

Elsewhere[92] is presented a "pedigree of causes" in which the several manifestations of the Marfan syndrome are related to the hypothesized, but, as yet, undefined fundamental defect of connective tissue.

The Skeletal Aspects (see Fig. 1 for the various body types encountered).—Dolichomorphism characterizes the skeletal abnormality of the syndrome. The victim often suggests the subject of an El Greco painting.* The extremities are long, and characteristically the lower segment (pubis-to-sole) measurement is in excess of the upper segment (pubis-to-vertex) measurement and the arm span in excess of the height. In general, the more distal bones of the extremities tend to demonstrate this excess length most strikingly. Arachnodactyly is the result (Fig. 3). At times the great toes are elongated out of proportion to the others (Fig. 3,*B*).[47,163] The ribs participate in the excessive longitudinal growth with formation of pectus excavatum (Fig. 1,*C*), "pigeon breast" (Fig. 1,*B*) or less symmetrical varieties (Fig. 4,*A*) of thoracic cage deformity. The bones of the skull and face are likewise affected with resulting dolichocephaly, highly-arched

*Astigmatism is thought to have been the basis for El Greco's distorted representations, as in "St. Martin and the Beggar" (National Gallery, Washington, D. C.)

palate, long, narrow face, and prognathism. There may be "spurring" of the heels as a result of excessive length of the os calcis.

Skeletal proportions are more important than actual height. It is true that these patients are often very tall. One patient was 6 feet tall at the age of 12 years.[30] Another patient[180] was 7 feet tall. The tallest patient encountered in our investigations was 6 feet 7 inches tall.

Redundancy and "weakness" of joint capsules, ligaments, tendons, and fascia is responsible for a large group of manifestations which include pes planus, genu recurvatum, hyperextensibility of joints, habitual dislocation of hips,[63] patella,[110] clavicles, mandible, and other joints, ganglia,* hernias, synovial diverticula,* kyphoscoliosis. The "flat feet" are often so advanced that the internal malleolus literally rest on the floor (Fig. 3,*D*). Kyphoscolosis can be very severe (Fig. 4,*B*). In rare instances, hemivertebra is responsible in part for spinal deformity.[90] At times, the spinal deformity has been thought to be due to Scheuermann's epiphysitis.[99] Even femoral hernias occur rather commonly in men with Marfan's syndrome, and diaphragmatic hernia has been present in some of our patients. Hydrocele is occasionally present.

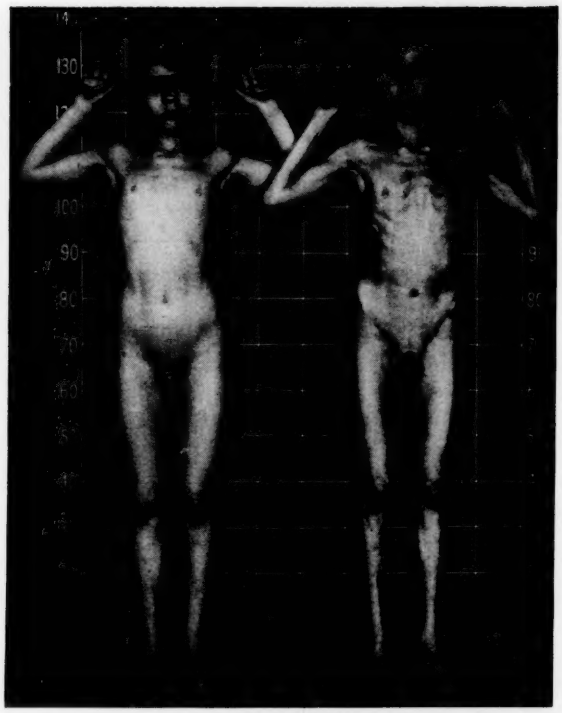
Muscular underdevelopment and hypotonia is a frequent[46,160] but by no means invariable feature. This feature has been so striking as to suggest a primary disorder of muscle in some instances. (The converse error of diagnosis—primary muscular dystrophy called Marfan's syndrome—has occurred in isolated instances.) It is probable that the muscular manifestations are secondary to the abnormality of bones and joints and to abnormality of the perimyal connective tissue and are not due to primary involvement of the muscle cell itself. This view is supported by the finding of a normal creatinine coefficient, an index of total muscle mass.[165]

Pronounced sparsity of subcutaneous fat is a striking feature of most cases (Fig. 1,*A* and *B*) and is not easily reconciled with a fundamental defect of connective tissue. In children, it may be that the rapid growth accounts for the failure to store fat. One patient, who was thin as a child, has become exceedingly obese in recent years (she is now 25 years old), due in large part to inactivity associated with the blindness produced by bilateral retinal detachment (Fig. 6). As demonstrated in Fig. 1,*G*, etc., others of these patients may have abundant subcutaneous fat.

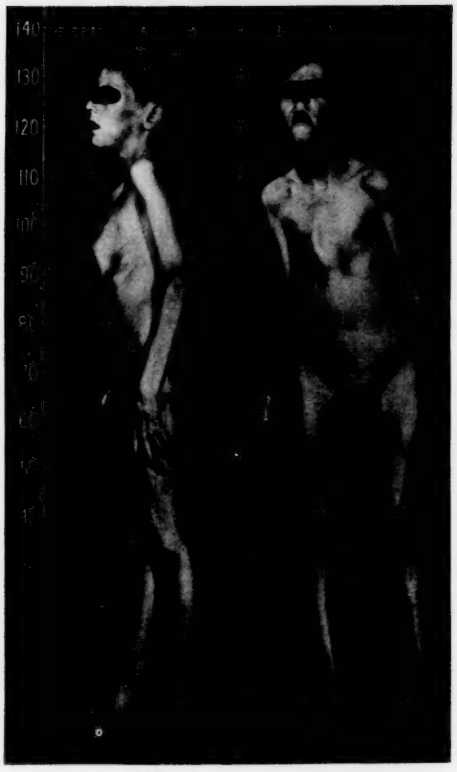
The Eye.—Ectopia lentis, almost always bilateral, is the hallmark of ocular involvement in this syndrome (Fig. 5). The suspensory ligaments, when visualized with the slit lamp, are redundant, attenuated, and often broken. The lower ligaments are more likely to be defective with displacement of the lens upward as the usual finding. The lens is often abnormally small[49,87,88] and spherical.

Myopia is usually present in rather high degree. The excessive length of the eyeball, resulting in myopia, appears to indicate involvement of the sclera, fundamentally a ligamentous structure, in the basic connective tissue defect. The scleral defect is occasionally expressed in the cornea as keratoconus or as megalocornea.[151]

*In one case,[14] a peculiar pelvic cyst communicating with the lining of the sacral canal occasioned difficulties in delivery.

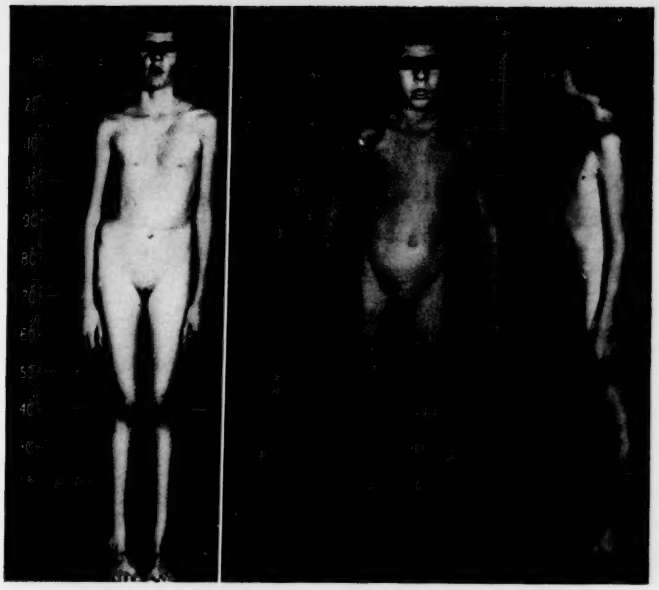


1,*A*.

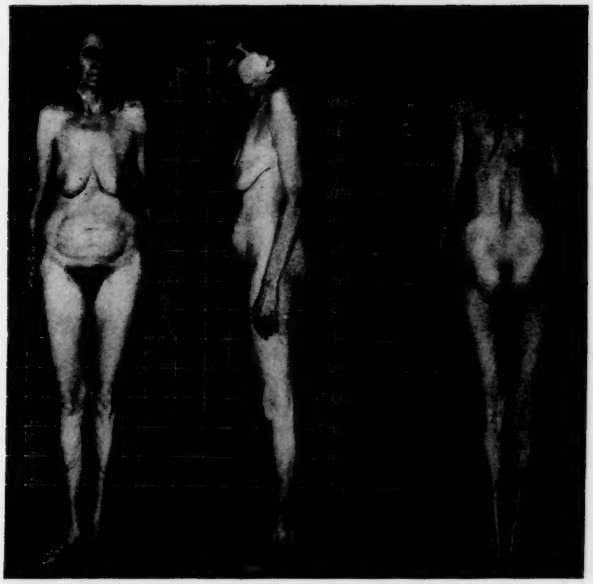


1,*B*.

VOL. 2 1955



1,*C*. 1,*D*.



1,*E*

Fig. 1,*A*.—Brothers, one with Marfan's syndrome. The one on the left is normal, aged 10 years. M.D. (A 59949), on the right, is only 8 years old. He shows ectopia lentis, contracture of the fifth fingers (see Fig. 3,*C*), heterochromia iridis (right iris, blue; left, light green), Horner's syndrome on left, lack of subcutaneous fat, high palate, scoliosis and thoracic deformity, abnormal electroencephalogram. This is probably a sporadic case (original mutation). Contracture of the fifth fingers (clinodactyly or camptodactyly) occurred in other patients of this series (e.g., J.A.M., A 65283).

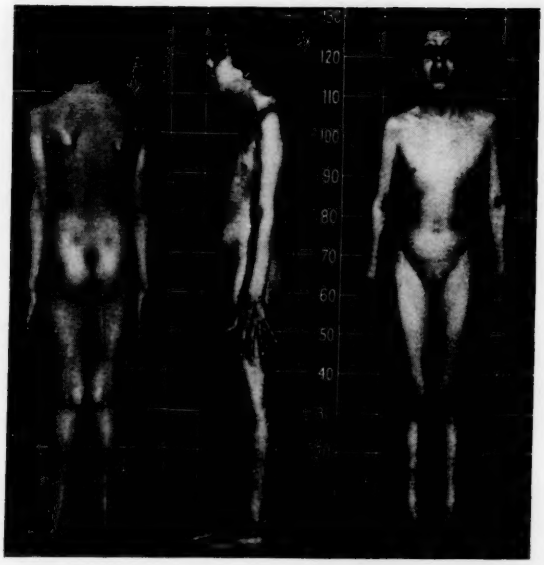
Fig. 1,*B*.—C.A. (B 9912; 692938) 7 years old. Pronounced pectus carinatum. Normal mentality. Nystagmus. Bilateral ectopia lentis. "Rocker-bottom" feet. Sparce subcutaneous fat.

Fig. 1,*C*.—M. McG. (A 92675), aged 7 years. Bilateral ectopia lentis. Severe pectus excavatum. Highly intelligent. Frequent respiratory infections. Loud systolic murmur of unclear origin. The mother has the full-blown syndrome and is sightless in one eye from spontaneous retinal detachment.

Fig. 1,*D*.—D.W. (B 8430), 50 months old. Is thought to have minimal dilatation of the ascending aorta and mitral regurgitation. Also has kyphoscoliosis and ectopia lentis. Parents appear unaffected but paternal great grandfather was 6 feet 7 inches tall.

Fig. 1,*E*.—M.P. (362804), 53 years old, the oldest patient with the Marfan syndrome I have had opportunity to examine. (One man with probable Marfan's syndrome was killed accidentally at the age of 82 years. He was still well preserved at that time. He was 75 inches tall and fathered at least two full-blown cases of Marfan's syndrome [see Fig. 2 of reference 92 for the x-ray of one] and four probably affected individuals out of sibship numbering twelve in all.) Extensive pedigree of Marfan's syndrome. Systolic crunch (extracardiac sound) present for many years.

1,*F*.



VOL.
2
1955

1,*G*.

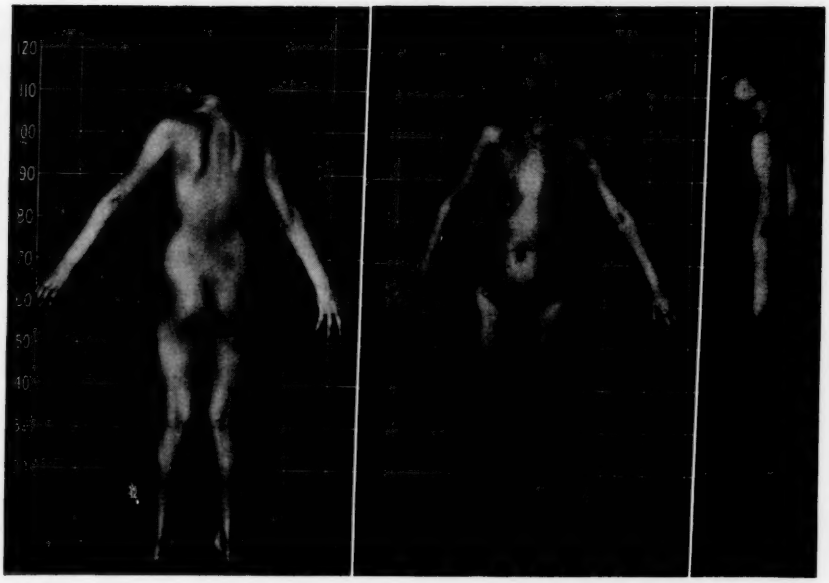


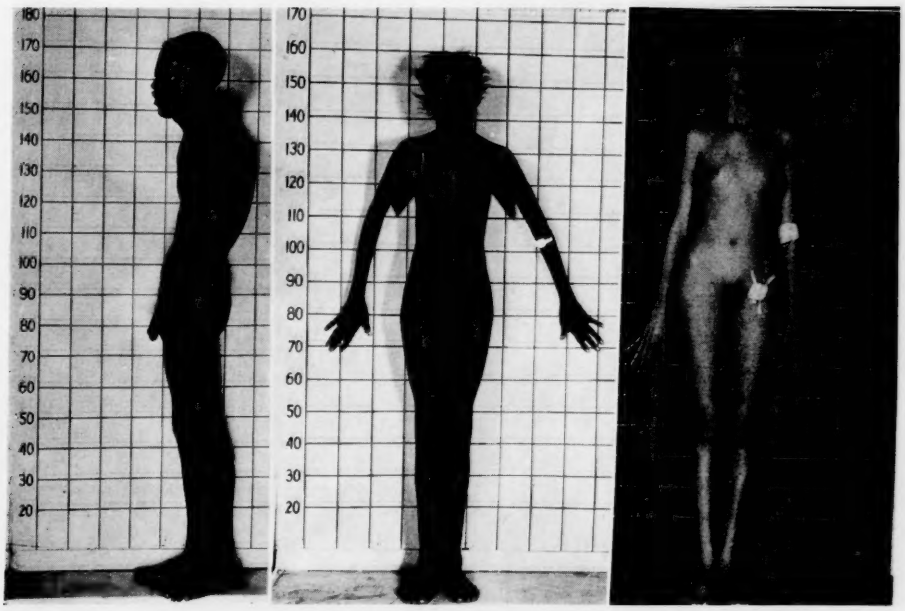
Fig. 1,*F*.—D.L.F. (516670), aged 7 years. The ptosis was thought to be part of the general muscular hypotonia which was so severe that amyotonia congenita was suspected when the patient was seen at the age of 4 years. Umbilical and bilateral inguinal hernias have been repaired surgically. The feet are very long, flat, and narrow. Kyphoscoliosis is evident. No ectopia lentis or ocular abnormality other than ptosis demonstrated. Intelligent.

Fig. 1,*G*.—J.A.L. (661948), aged 5 years, 8 months. Ectopia lentis. Probably *de novo* mutation. Shown very well is the eversion of the feet with low position of the internal malleolus ("rocker bottoms"). Child bright, but highly nervous.

The sclera may be impressively blue in the Marfan syndrome.[23] Clouding of the cornea occurs occasionally. How much of this is a primary element of the connective tissue disease and how much a result of the secondary iritis and glaucoma is difficult to state.

Spontaneous retinal detachment occurs with what is probably an unusually high incidence and is a frequent complication of lens extraction. Retinal detachment is probably related to the long myopic eyeball and therefore indirectly to the connective tissue defect; that there is a more direct relationship is strongly suspected[72] because of the high incidence in Marfan's syndrome even without more than a moderate degree of myopia. The pupil is often difficult to dilate in Marfan's syndrome and the dilator muscle appears to be hypoplastic.[137]

The ectopia lentis per se would probably represent relatively little impairment of vision. The severe myopia (20 diopters in Boerger's[24] case), the retinal



A. *B.* *C.*

Fig. 2.—Confusing and uncertain cases.

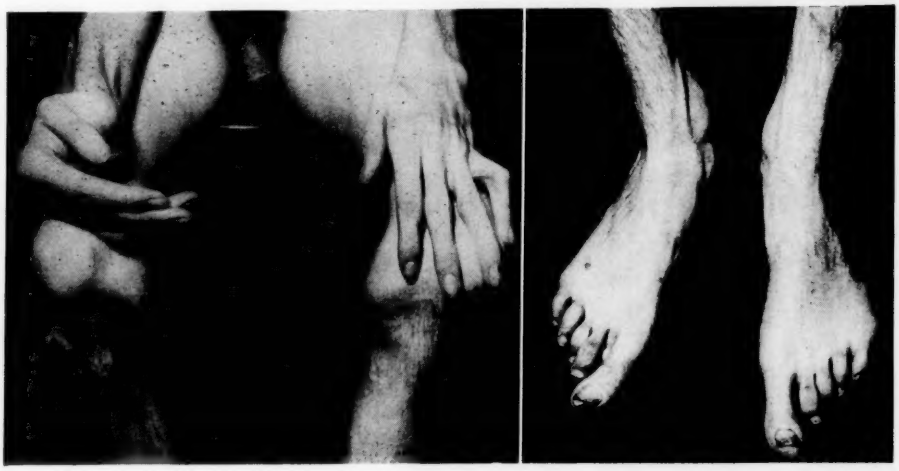
A,—L.M. (611512), 45-year-old Negro man, sustained an injury to his chest one year before this photograph. Shortly after the accident he began to have paroxysmal nocturnal dyspnea and was found to have profound aortic regurgitation. The left ventricle and first portion of the ascending aorta are enlarged. Spinal deformity has become progressively more impressive in this patient. There is no ectopia lentis. For geographic reasons, the family investigation is not entirely satisfactory, but no suspicions of the Marfan syndrome are present on this score either.

B,—W.F. (651498), 12 years old. Two years previously acute encephalitis occurred, followed by mental deterioration with positive neurologic signs. No ectopia lentis. The mother, who is normal, has the same skeletal proportions.

C.—R.G.W. (697871), only 13 years old. Myopic astigmatism but no ectopia lentis. Loud precordial systolic murmur of unidentified cause. Cardiac catheterization unrevealing. The extreme dolichostenomelia and the pelvic asymmetry make Marfan's disease very likely. The diagnosis cannot be established in the absence of positive family history or ectopia lentis.

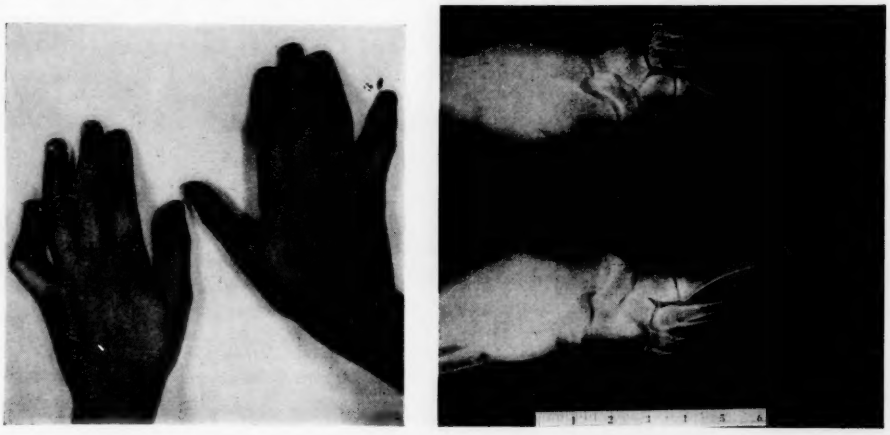
detachment, and the iritis and/or glaucoma which may result from the ectopia lentis are often responsible for severe limitation of visual acuity or even total blindness. The lens may become secondarily cataractous.

I was previously suspicious that estimations that only 50 to 70 per cent of cases of clean-cut Marfan's syndrome have ectopia lentis were incorrectly low as a result of inadequate examination of the eyes and that virtually 100 per cent of cases would display at least minor redundancy of the suspensory ligament if subjected to maximal mydriasis and slit-lamp examination. It may be true that the first estimate above is too low. We have now observed patients with



A. *B.*

Fig. 3,*A* and *B*.—H.W. (464314), 17 years old. *A*, Died suddenly at home eighteen months after this picture. Ectopia lentis. Referred because of spontaneous retinal detachment. Striking arachnodactyly with partial contractures of fingers. Children delight in doing contortions with their fingers but should not be permitted to do this since they probably do themselves harm thereby. *B*. Extraordinary length of the great toes is well demonstrated. Even more pronounced excess of length of great toe shown by case illustrated by Whitfield, Arnott, and Stafford.[180]



C. *D.*

Fig. 3,*C*.—Flexion deformity (clinodactyly) of fifth fingers, particularly on left. Taken at age of 38 months in M.D. (A 59949), who is shown at a later age in Fig. 1,*A*. Other patients in this series have shown this feature.

Fig. 3,*D*.—X-rays of feet in case with so-called "rocker bottoms", i.e.; pronounced flat feet. Patient J.M. (544088); see also Fig. 12.

VOL. 2 1955

A.

B.

Fig. 4,*A*.—Asymmetrical pigeon-breast type of chest deformity in 14-year-old boy (J.S., 543026) will full Marfan's syndrome. This particular type of anterior chest deformity seems to be of frequent occurrence in Marfan's syndrome. At the age of 18 years, the patient was 73 inches tall. Incomplete right bundle branch block is present. The patient's father was 6 feet 7 inches tall, and at the age of 28 years died suddenly on a street bus. He had been observed for two years for aortic regurgitation which had been considered rheumatic in origin.

Fig. 4,*B*.—Marked spinal deformity in 14-year-old F.D., one of first cases of aortic aneurysm with arachnodactyly reported by Baer et al.[11] (See reference 11 for photographs of the external appearance of this patient.)

Fig. 5.—Dislocated lens in R.C. (241676), then aged 6 years. Chronic "malnutrition," bilateral inguinal hernias, slow physical development, diastasis recti. At the age of 22 years he was 73 inches tall, weighted 150 pounds, and wore a size 12 AAA shoe. He was inducted into the army and served six months before his eye condition was ascertained. The slight divergent strabismus is evident. Also one can make out the forward bulging of the nasal portion of the right iris with failure of more complete dilatation of the pupil in that segment because of anterior synechiae.

Fig. 6.—L.T. (221183), at the age of 8 years (*A*), at the age of 23 years (*B*). At 8, the patient is virtually the same height as M.D. (in Fig. 1,*A*), also 8 years old. The patient became almost completely blind from bilateral retinal detachments. With the inactivity associated therewith, she became very obese, as demonstrated in *B*. White atrophic striae appeared on the shoulders, upper arms, hips, and thighs, as has been described previously in obese patients with Marfan's syndrome.[173] The patient probably had rheumatic fever with carditis as a child, but no residua are detectable. She has demonstrated, in addition to ectopia lentis, accessory rudimentary sixth digit bilaterally, highly arched palate, pupils which react poorly to mydriatrics. *C*, Prison photograph of the proposita's father (B.R.). The character of the spectacles suggests hyperopia, an unusual although occasional finding in the Marfan syndrome. He had several admissions to the Norfolk, Virginia, General Hospital (A 46772) for hernia repair, for acute dissection of the aorta (age 38), for varicose veins, for pain in the low back. The final hospital admission was to the St. Luke's Hospital, Newburgh, New York, because of severe pain up and down his back. Profound aortic regurgitation and a pulsating abdominal mass were discovered. Serologic tests for syphilis were negative. The patient died suddenly (age 39). Autopsy revealed old dissection of the aorta with recent rupture into the pericardial cavity and tamponade.

VOL. 2 1955

advanced Marfan's disease with characteristic habitus, involvement of other members of the family, and dissection of the aorta with autopsy demonstration of pathognomonic changes in the media, who did not have ocular abnormality on most careful examination. This part of the syndrome, it seems, may be suppressed in a given family. This is consonant with the frequent observation that the pattern of expression of this syndrome seems to be similar in affected members of one kinship.

A. *B.*

Fig. 7.—In *A* and *B* are shown a normal individual (III 12) and her five siblings affected by the Marfan syndrome (III 15, III 14, III 13, III 11, and III 8). Also shown in *B* is a 4-year-old affected member (IV 13) of the next generation, son of III 8. (The numbers refer to those in a pedigree published elsewhere.[92]) Individual III 11 subsequently died of bacterial endocarditis engrafted on a mitral valve probably affected by connective tissue changes of the Marfan syndrome.[92] There was chromatropic degeneration of the ascending aorta and pulmonary artery as well as advanced congential cystic disease of the lungs. Individual III 14 is 78 inches tall. (History numbers: 176836, 176837, 176838, 103632, 637693, 637694, 392843.) The father of the sibship shown in *A* and *B* (W.R., 101043) died suddenly at home at the age of 43, presumably of aortic rupture. He was well known as a case of Marfan's syndrome and had been under treatment for a cardiac ailment with aortic regurgitation for about two years.

The Cardiovascular System[61,92].—Since most of the early autopsies in cases of this syndrome were in infants and children, and since interatrial septal defect was found (probably largely by coincidence) in several of the cases, this malformation and "congenital heart disease" in general came to be considered the usual form of cardiovascular involvement. As more adult cases were recognized, it became apparent (1) that an inborn weakness (with subsequent degeneration) of the media of the aorta and main pulmonary artery is of much more statistical importance and more functional importance in the individual patient, and (2) that this abnormality is an abiotrophy, not a congenital malformation. The abnormality of the media may result in diffuse dilatation of the ascending aorta or pulmonary artery, in dissecting aneurysm, or in a combination of dilatation and dissection. Striking involvement of the pulmonary artery occurs[11,92,166] much less commonly than the corresponding involvement of the

aorta. However, a clinical picture like that of so-called[77] "congenital idiopathic dilatation of the pulmonary artery" may occur, as well as dissecting aneurysm of the pulmonary artery.[5,182]

In the aorta, dilatation usually begins in the aortic ring and intrapericardial portion of the ascending aorta as suspected clinically and as demonstrated in cases dying before further progression of their disease.[91,175] This, together with stretching of the aortic cusps, may produce profound aortic regurgitation before clear roentgenologic signs of aortic dilatation are present (Figs. 8,*D*, 12,*C*, and 13). If syphilis, rheumatism, and bacterial endocarditis can be excluded, traumatic rupture of an aortic cusp is often suspected.[15,92]

Furthermore, a deceptive prominence of the pulmonary conus and main pulmonary artery may be produced by the dilated aortic base and compound the confusion.[11,92,112] In a recent case (J. M., J. H. H. 544088) the aneurysm at the base of the aorta apparently caused partial obstruction of outflow from

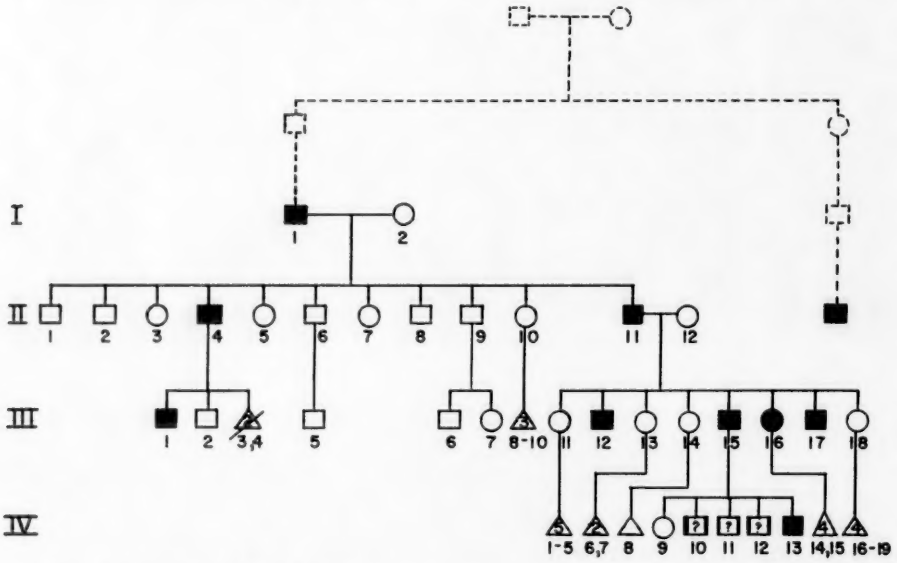


Fig. 8,*A*.—Pedigree of the F. kinship.

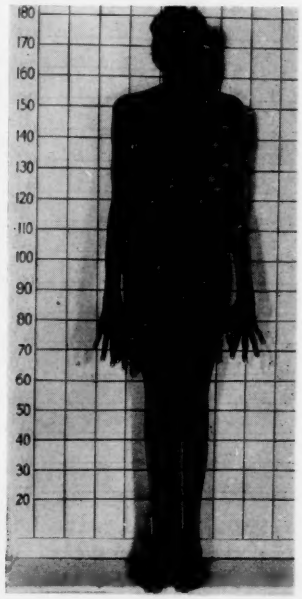
II. 1. Charles. Died of acute indigestion at age 47. 4. Grant. About 6 feet 4 inches tall, died at age 35; two of his children died at 8 and 12 months, respectively. 8. Henry. Examined; unaffected.

III. 1. James Aloysius. Typical Marfan syndrome; 6 feet 4½ inches tall, size 13 shoe; ectopia lentis with secondary cataract formation; complete loss of vision from bilateral detachment of retina; early aortic diastolic murmur. 11. Josephine. Examined; unaffected. 12. Clarence (352936). At age of 32 years found to have complete detachment of right retina; left lens dislocated and cataractous; partial detachment of left retina; died at age of 34 years, 18 days after onset of congestive heart failure attributed to syphilitic heart disease because of finding of aortic regurgitation. 13. Blanche. Examined; unaffected. 15. Theodore (see Fig. 8,*B*). Typical Marfan syndrome with cardiovascular death. 16. Leona (see Fig. 8,*C*, *D*, and *E*). Typical Marfan syndrome with autopsy confirmation of dissecting aneurysm of the aorta. 17. James Leon (424834). Ectopia lentis with severe secondary iridocyclitis and glaucoma; detachment of right retina; 75 inches tall, weight 172 pounds, kyphoscoliosis, variococele; lax sternocleidomastoid joints, mobile patellae, flat feet, cardiomegaly with globular shape by x-ray; no murmurs. This individual and Theodore and Clarence "always looked just like twins." Positive serologic test for syphilis.

IV. 9. Mary, b. 1939, probably normal. 10. Leroy, b. 1940, probably normal. 11. James, b. 1944, peculiar shape of head. 12. Edward, b. 1945. Same peculiar shape of head. 13. D. Theodore, b. 1950. Definite Marfan syndrome: 38 inches at 30 months; long peculiarly shaped head.

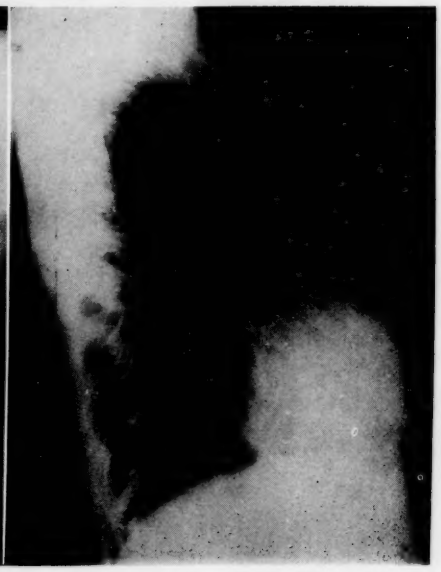
VOL. 2 1955

8,*B*.



8,*C*.

8,*D*.



8,*E*.

Fig. 8,*B*.—Carnival snapshot of III 15 (T.F.). Arachnodactyly is evident. In his left hand he holds his spectacles. He died suddenly at the age of 33 years, two weeks after consulting a physician for exertional dyspnea. Aortic regurgitation had been discovered. An optometrist reports that he had "a decided miosis and the opthalmoscopy showed the media to be cloudy." He was myopic. Worked as farm laborer until a few days before death.

Fig. 8,*C*.—L.F.Y. (690823), 33 years old. Patient died of effects of severe aortic regurgitation. Autopsy revealed characteristic changes in the media of the aorta and pulmonary artery with old dissecting aneurysm of the ascending aorta. (See Fig. 14B, in reference 96 for a drawing of the aorta with old dissecting aneurysm.)

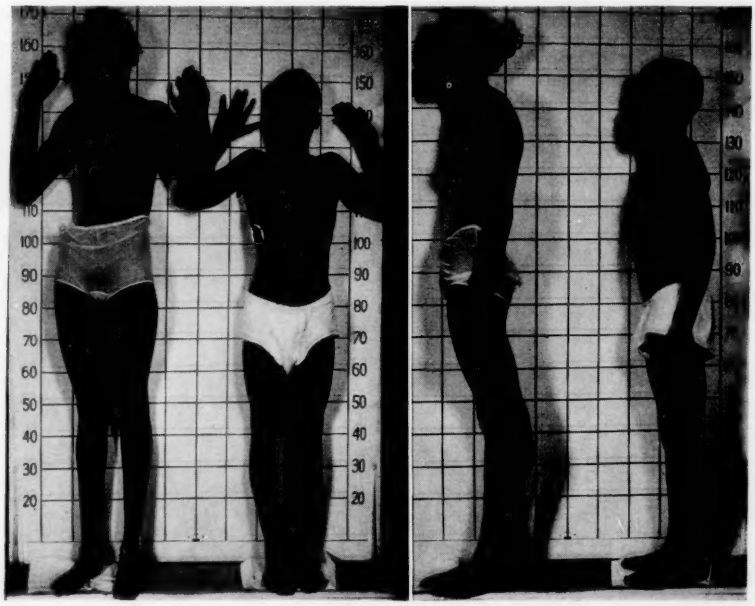
Fig. 8,*D* and *E*.—Posteroanterior and lateral views of chest in L.F.Y. It is remarkable that enlargement of the aorta is not more evident. In lateral view there is opacification behind the sternum.

the right ventricle with the development of progressive right axis deviation by electrocardiogram. In these cases, the second heart sound in the pulmonary area may be unusually loud due to close proximity of the pulmonary artery to the anterior chest wall.

Aortic dilatation is usually progressive. The patient may be free of symptoms for five or more years after the development of aortic regurgitation, but once angina pectoris or symptoms of left ventricular failure have developed, he seldom lives more than two years. On the whole, the prognosis is quite similar to that of syphilitic aortitis.[174] In fact, the similarities of the two diseases are in many respects striking. It seems to matter little whether the defect of the media, specifically the elastic lamellae, is produced by the spirochete from without or the mutant gene from within.

The onset of aortic dilatation may be as early as the fifth year or as late as the sixth decade. The oldest reported patient with aortic insufficiency without

VOL. 2 1955



A. *B.*

Fig. 9,*A* and *B*.—Fourteen-year-old S.S. (366788), II 6 of the pedigree (*C*), and her normal 12-year-old brother, II 7. Note the kyphoscoliosis, genu recurvatum, excessively long legs, strabismus. Ectopia lentis is present.

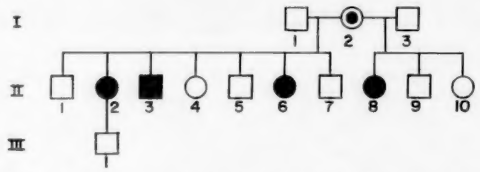


Fig. 9, *C*.—This pedigree illustrates how submerged the manifestations of Marfan's syndrome can be. Individual I 2 had had at least three affected offspring by one husband and one affected offspring by a second husband. Both husbands are unequivocally normal from the skeletal, ocular, and vascular points of view. The mother is 5 feet 8 inches tall, is moderately long of limb, is poorly muscled, and is severely myopic (6 D.), but has no ectopia lentis by careful ophthalmoscopic examination. (For the last I am indebted to Dr. J. E. Mishler of Atlantic City, N. J.). These manifestations are consistent with *forme fruste* of the Marfan syndrome but would not be recognizable as such without the knowledge of this pedigree.

evident aortic dilatation was 56 years of age.[76] In one reported case,[162] dilatation of the ascending aorta with aortic regurgitation and marked left ventricular hypertrophy resulted in the death of a 10-month-old infant; in another case,[146] death occurred at 55 years.

The dilatation is almost always confined to the ascending aorta proximal to the innominate artery. However, in Case 3 of Thomas and co-workers,[159] the descending aorta was also involved. Furthermore, at least two instances of fusiform aneurysm of the abdominal aorta have been described recently.[82] Dissection exclusively in the aorta beyond a mild coarctation at the usual site has been described.[168] Several cases (e.g., reference 106) have had cystic medial necrosis, dissection, and internal tears in the abdominal as well as the ascending aorta.

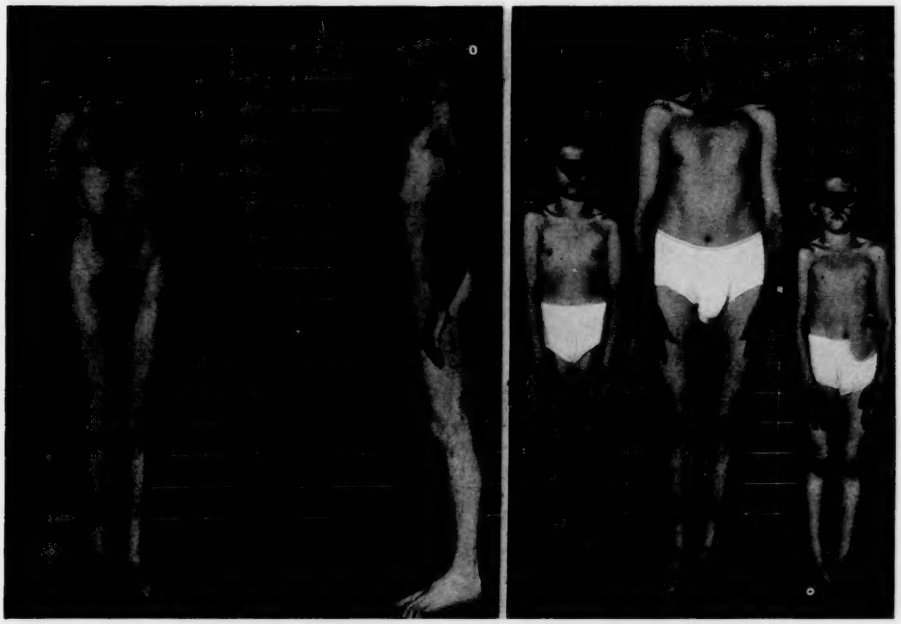


Fig. 10. Fig. 11.

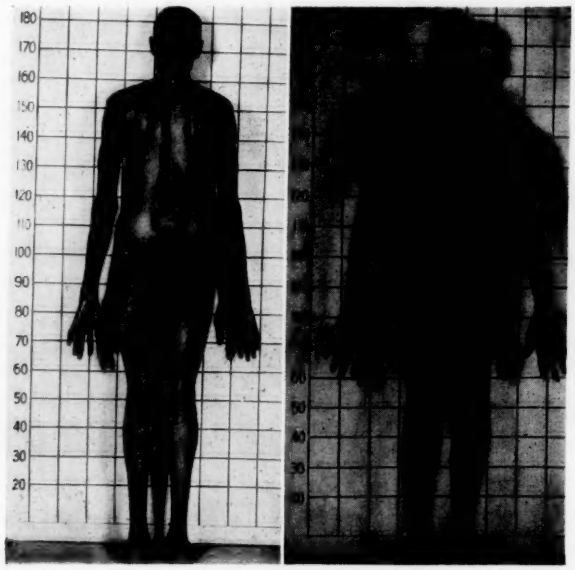
Fig. 10.—C.H. (687485), 28 years old. Ectopia lentis. Lenses correcting for aphakia worn from age of 5 years. Brother, father, two paternal aunts, and two cousins are living and have the Marfan syndrome. Paternal grandmother and great grandmother likewise had it. Father blind in both eyes and aunt blind in one eye from secondary glaucoma. Patient in Army for 45 months. Note deformity of knees. This and many of the other members of this group of photographs makes it clear that on superficial inspection the habitus may not seem impressively or abnormally dolichostenomelic.

Fig. 11.—Father, E.C., and two children, Anna (593933), aged 9 years, and Robert (441759), aged 7 years, all with ectopia lentis and skeletal proportions, albeit not striking, consistent with the Marfan syndrome. The father's brother had had a "leaky heart" for several years and died suddenly at the age of 35 years.

By examining a large number of patients with ectopia lentis and by studying the relatives of established cases of Marfan's syndrome, we have now discovered five patients who appear to be in the early stages of aortic dilatation with aortic regurgitation.[92] In none is there yet evident dilatation of the ascending aorta (Fig. 13).

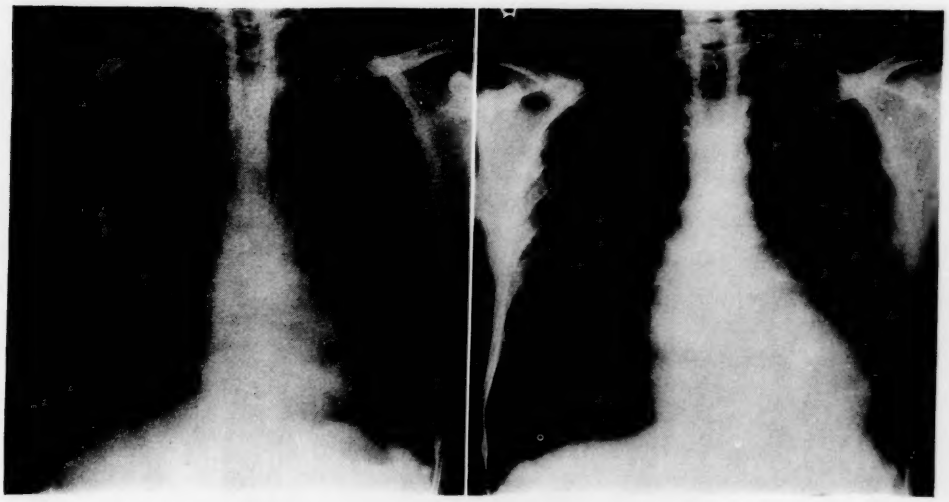
Dissecting aneurysm may occur as the first aortic complication or may be superimposed on diffuse dilatation of the ascending aorta.[98] There is evidence that dissection may occur in the first decade of life; the oldest reported case of dissecting aneurysm in Marfan's syndrome was that of a 52-year-old woman.[48] The patient may survive for a number of years after first dissection of the aorta and even after a "leak" into the pericardium. Because of the aortic regurgitation which results either from the dissection itself[64,127] or from the associated dilatation of the aortic ring, confusion with rheumatic[83] or syphilitic[60] heart disease is frequent. In a recently autopsied case at this hospital, leaking of the original dissecting aneurysm into the pericardial sac led to the misdiagnosis of tuberculous pericarditis. The patient survived five years after the first pericardial episode. Dissection apparently occurs with increased frequency during pregnancy.[107,141,143] In chronic dissecting aneurysm of the aorta, there may be little enlargement of the aorta evident on x-ray (see Figs. 8 and 12). In our experience, when full family investigations are made, Marfan's syndrome is found to be the leading "cause" of dissecting aneurysm in persons under the age of 40 years. Gore[57] reported that 3 of 22 cases had arachnodactyly. This, however, was not a detailed clinicogenetic study.

VOL. 2 1955

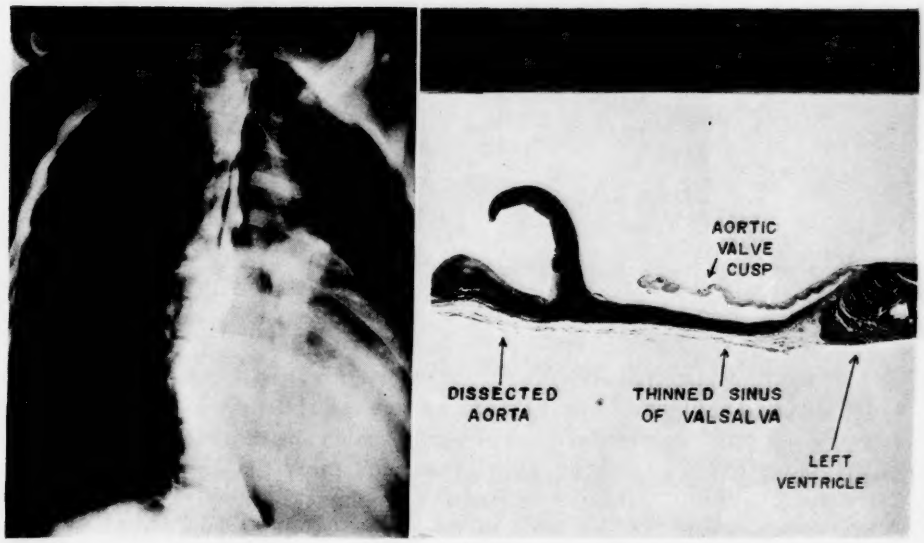


A. *B.*

Fig. 12,*A* and *B*.—Brothers with the Marfan syndrome without ocular manifestations. *A*, J.M. (544088) had genu valgus, severe pes planus, dolichostenomelia but no ectopia lentis. In 1950 an episode of chest pain accompanied by pericardial friction rub was interpreted as pericarditis and treated for presumed tuberculous etiology. Signs of aortic regurgitation developed thereafter. In 1953, there occurred at least one other episode of chest pain with pericardial friction rub. The effects of aortic regurgitation became progressively more severe and were the cause of death in April, 1955, at the age of 30 years. Autopsy revealed superannuated dissecting aneurysm of the ascending aorta and dilatation of the aorta above the aortic ring. The aorta had apparently "leaked" into the pericardial sac almost five years before death. (Known to us is a second case [S.T., 691351] in which the patient was still living following leakage about 18 months before. The diagnosis of Erdheim's disease was established at operation for aneurysm of the ascending aorta.) *B*, W.M. (702409), aged 27 years, was discovered to have aortic regurgitation when examined in connection with his brother's illness. He had dolichostenomelia and spinal curvature. Although the left ventricle is large, no dilatation of the aorta is demonstrable. He is asymptomatic.



C. *D.*



E. *F.*

Fig. 12,*C*—*E*.—Series of x-rays in J.M. *C*, Taken in 1950 about one month after the initial episode of leakage into the pericardial sac. *D* and *E*, The appearance in the last year of life. Enlargement of the aorta is not impressive in *D*, but the main pulmonary artery is prominent. In the right anterior oblique (*E*) the barium-filled esophagus is displaced by a structure which necropsy demonstrated to be an aneurysm of the sinus of Valsalva. In the left anterior oblique (not shown here), again the aorta does not appear particularly dilated.

Fig. 12,*F*.—Microscopic section (×4) of aortic valve area in J.M. (see *A*). The old dissection, the thinning of the sinus of Valsalva, and the minor fibrous thickening of the aortic valve are demonstrated.

Involvement of the aortic cusps has already been described. The mitral cusps and chordae tendineae may be redundant with resulting mitral regurgitation. Subacute bacterial endocarditis may become engrafted on the valvular abnormality.[92,108,170] Murmurs of obscure origin are frequently encountered. Some may be on the basis of redundant chordae tendineae with incompetence of atrioventricular valves. Extracardiac clicks and other extraneous sounds are frequent because of the thoracic deformity.

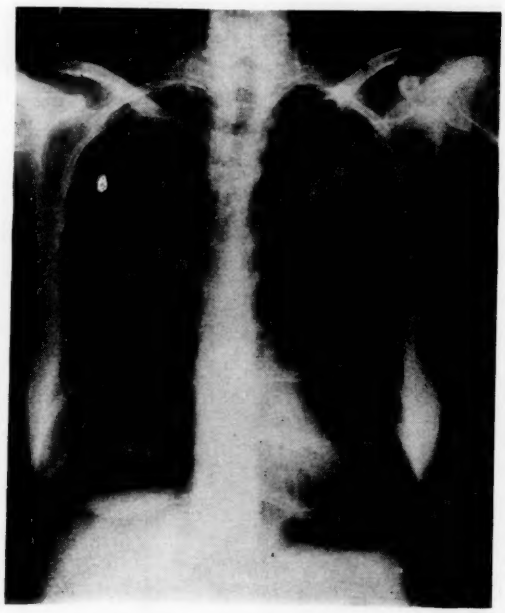


Fig. 13—X-ray of chest in M.B. (697662), 46 years old. Ectopia lentis, moderate dolichostenomelia, spinal curvature. Although the patient is asymptomatic and the cardiovascular silhouette is normal, an aortic diastolic murmur is present.

Occasionally the pathophysiologic effects of interatrial septal defect dominate the clinical picture. Notwithstanding careless statements of previous reviews, no autopsy-confirmed or even clinically convincing case of interventricular septal defect has been reported. In Cockayne's case[33] the diagnosis was only suspected clinically. There is a report[86] of possible tetralogy of Fallot with Marfan's syndrome. In two cases of tetralogy of Fallot which have come to my attention,[92] there are stigmata suggestive of the Marfan syndrome, but the absence of involvement of other members of the family and the failure of ectopia lentis to be found in the patients make the diagnosis of the Marfan syndrome uncertain. I am inclined to think that these are not cases of the Marfan syndrome. In yet another case (Fig. 16), striking dolichostenomelia, congenital clouding of the cornea and large interventricular septal defect are associated. Four siblings, two older and two younger, are unaffected as are all other members of the family, in so far as can be determined. Furthermore, no abnormality of the lens is detectable. This case seems most likely the result of infection or other abnormality of the intrauterine environment.

VOL. 2 1955

Much has been written about cardiac disability in pectus excavatum.[45,48,104,157] Furthermore, since originally proposed by Flesch[50] in 1873, excessive longitudinal growth of the ribs has been thought to be the mechanism in many cases. As stated above, this appears to be the pathogenesis of the pectus excavatum in the Marfan syndrome. The hereditary nature of pectus excavatum has been appreciated.[114,135,147,153] Many times the patients with pectus excavatum are described as being unusually tall and thin with spinal curvatures. Despite all these considerations, it has not been properly appreciated that the pectus excavatum may be but one manifestation of a generalized disorder of connective tissue in which direct involvement of the cardiovascular system may occur. Elsewhere,[92] we have presented the case of a 24-year-old man with severe pectus excavatum, who died of rupture of the aorta shortly after surgical repair of the chest deformity.[21] Autopsy revealed aortic changes typical of the Marfan syndrome. An aortic diastolic murmur had been present before operation.

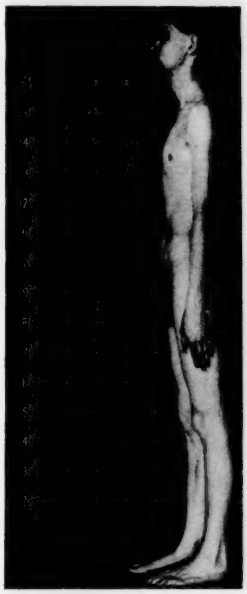


Fig. 14.—The patient, R.R. (704121), aged 30 years, has clouding of the cornea, dolichostenomelia, and probable large interventricular defect. It is likely that this is due not to Marfan's syndrome but rather to intrauterine insult of unidentified variety.

In the surgical literature, there are two cases which may have been instances of the Marfan syndrome. One patient[83] was 6 years old and was described as having "systolic and diastolic murmurs and cardiac incompetence." The other,[125] 23 years old and 74 inches tall, had congestive heart failure and atrial fibrillation and was specifically described by his physician as thin, gangly, loose-jointed, and round-shouldered. In another instance, a case reported by Sweet,[158] the patient has been discovered to have typical Marfan's syndrome.[179]

The cardiovascular aspects of this syndrome have been presented in greater detail elsewhere.[92]

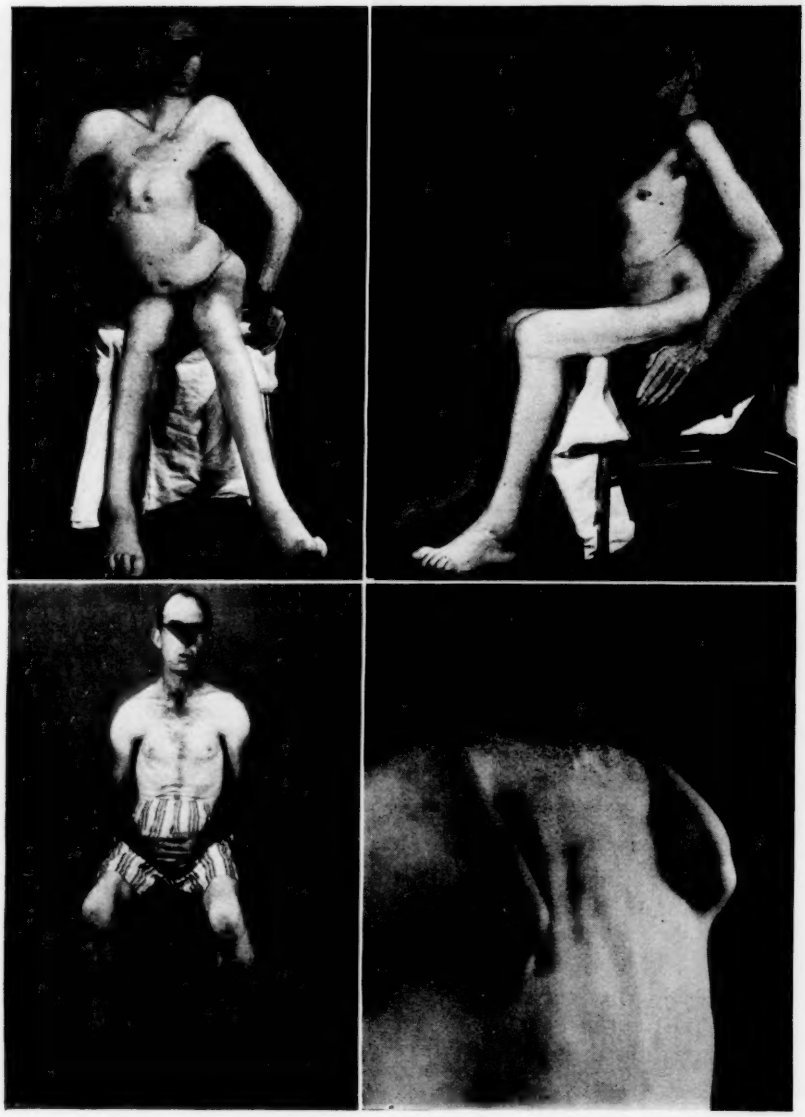


Fig. 15.—*A* and *B*, W.M. (Mary Imogene Bassett Hospital No. 54659) was thought to have Marfan's syndrome because of aortic regurgitation, severe spinal deformity, and arachnodactyly. Clinical evidence for bacterial endocarditis was present. At autopsy the heart lesions appeared to be rheumatic with superimposed valvular infection. (I am indebted to Dr. Jas. Bordley, III, for knowledge of this patient and permission to include him here.) Numerous pigmented nevi were present in this patient.

C and *D*, D.M., brother of W.M. The finding of muscular dystrophy in this brother makes it likely that W.M. (in *A* and *B*) likewise had muscular dystrophy. The disease trait appears to be recessive in this family. In D.M. note the wasting of the upper arms, especially the left, the asymmetry of the face in whistling, the winging of the scapulae. There is no arachnodactyly. Spinal deformity as severe as that in W.M. is sometimes seen with muscular dystrophy.[150] (The writer is indebted to Dr. Chas. Ellicott for studying this patient.)

VOL. 2 1955

A.

B. C.

Fig. 16.—Experiments conducted by Dr. James R. Brayshaw,[28] as student at The Johns Hopkins University School of Medicine.

A, Deformity and pathologic fracture of spine and other bones in rat fed seeds of *Lathyrus odoratus*.

B, Dissecting aneurysm of the aorta with rupture in rat fed seeds of *Lathyrus odoratus*. Shown is the dissection of the media and the large mediastinal hematoma. Elastic tissue stain. The elastic lamellae are black. (×10; reduced 1/5.)

C, Same at higher magnification. On the left below, the wall of the aorta is grossly scarred through almost its entire thickness. (×30; reduced 1/5.)

Other Manifestations.—Special attention is directed to certain manifestations which were indicated by dashed lines in the "pedigree of causes" presented elsewhere[92]: e.g., in the cardiovascular system, coarctation of the aorta,[49,92,168] patent ductus arteriosus,[9] and interatrial defect; in the skeletal system, spina bifida occulta,* hemivertebra, cleft palate[130]; in the eye, microphakia, hypoplasia or aplasia of the dilator-pupillae muscle, coloboma lentis. These are not among the more common manifestations, yet they occur sufficiently often in the Marfan syndrome to be considered more than coincidental associations. Their occurrence is difficult to reconcile with a unitary theory of a connective tissue defect unless one assumes that the presence of said defect during embryogenesis provides an abnormal environment in which these anomalies, congenital malformations in the usual sense, occur with increased incidence. In accordance with this last not improbable proposition, these particular manifestations can be considered *secondary* ones.

The coarctation has never, to my knowledge, been of functional significance. There is no reason, however, why it might not be in occasional instances. Dissecting aneurysm occurs with increased frequency in coarctation[67] and although the hypertension is doubtlessly a contributing factor, the possibility of a connective tissue abnormality being responsible for both the coarctation and the dissection must be considered.

Whether deafness is a specific manifestation of the Marfan's syndrome and if so, what its mechanism is,[87] cannot be stated at present. It is said to occur in 6 per cent of cases.[123]

Pulmonary malformations are described in autopsy reports and various pulmonary complications in clinical reports.[63,78,92,111,118,124,136,161] Repeated spontaneous pneumothorax has been described.[4,75,78]

Occasionally congenital cystic disease of the lung probably occurs as an integral part of the Marfan syndrome. In patient M. R. (J. H. H. 176836; see Fig. 7) very extensive disease of this type was discovered at autopsy. The stillborn child of this patient showed abnormal lobation of the lungs but no congenital cystic disease. Without an exhaustive review of the literature, it was possible to find three cases of cystic disease of the lung in which stigmata suggestive of the Marfan syndrome were described:

1. A 26-year-old male medical student (Case 9 in reference 111) had had three attacks of spontaneous pneumothorax. He died following an attack of severe chest pain. Dissecting aneurysm of the aorta with rupture into the pericardium was discovered. Histologically there was cystic medial necrosis. Both lungs showed diffuse cystic changes regarded as congenital.

2. A 26-year-old housewife (Case 13 in reference 111) with striking dolichostenomelia had had increasing dyspnea and, at the end of her second pregnancy, frank congestive failure. X-ray showed dilatation of the outflow tract of the right ventricle; EKG showed right axis deviation and the so-called P-pulmonale. Post-mortem examination disclosed diffuse cystic changes in both lungs and widely patent foramen ovale.

3. A 12-year-old child[132] was found at autopsy to have multiple simple cysts throughout both lungs, patent ductus arteriosus, aneurysm of the pulmonary artery, and anomalous coronary artery.

*Encephalocele in the forehead area occurred in one patient. Internal hydrocephalus is also reported.[113,124]

VOL. 2 1955

Congenital cystic disease is probably a secondary component of this syndrome; i.e., the presence of the connective tissue defect during embryogenesis conditions its development but is not as directly responsible for it as for some of the other manifestations. The Marfan syndrome can join xanthomatosis[148,164] and tuberous sclerosis[18,19] in the group of systemic abnormalities associated with a type of cystic disease of the lung.

There are other manifestations which occur less frequently, often in no more than single reported cases, than those termed "secondary" above. In the case of these, it is more likely that the anomaly occurs only coincidentally with the bona fide features of Marfan's syndrome. When the case in question is a sporadic one, it may be valid to assume that the mutagenic factor might have caused more than one mutation simultaneously. Furthermore, in a given family, if the anomaly in question occurs in only one of the persons affected by Marfan's syndrome, or, better yet, if the anomaly also occurs in one or more members of the family unaffected by the Marfan syndrome, the manifestation in question should not be considered part of the Marfan syndrome.

Contrary to previous emphasis,[36,87,113,140] mental retardation is not, in my opinion, a component of this syndrome. Usually the patients are at least as bright as their siblings. Sometimes their innate intelligence is not fully realized because of the limitation of opportunities imposed by severe visual impairment and other physical handicaps. In severe sporadic cases in infants and children, there may be mental retardation but this has, in my opinion, a separate basis, possibly an independent mutation. Another basis for confusion is the fact that a picture including arachnodactyly and suggesting the Marfan syndrome occurs with acquired developmental abnormalities such as rubella and other maternal illness, maternal exposure to x-ray, and rh incompatibility. These patients are likely to show mental retardation.

INCIDENCE AND INHERITANCE

The sexes are equally affected.[91,123] The aortic complications do seem to occur more frequently in men.[92] Manual labor may be responsible for this. There is no racial or subracial concentration of cases. The syndrome has been reported in Negroes,[53,92] Chinese,[31,66] Japanese,[168] Hindu,[20] and Jews.[91] It has, furthermore, been reported in natives of virtually every European country. Its incidence in the American Negro is probably essentially the same as in the white population. It has occured in American Indians.[56]

It is an uncommon, but by no means rare, disorder. The incidence of the Marfan syndrome is certainly far greater than the general conception of the medical public. The connective tissue defect of the Marfan syndrome is the leading cause of dissecting aneurysm of the aorta in the younger decades. There is reason to believe that there is an appreciable number of very mild cases (*forme fruste*) in whom the connective tissue defect has little or no effect on health or longevity.

Preposterously high estimates of the number of sporadic cases (those derived presumably from *de novo* mutation), as opposed to inherited cases, have been made. My own experience would indicate that no more than 15 per cent of all

cases are new ones. Higher estimates, up to 70 per cent by some writers, are the result of incomplete family studies. How often this mutation occurs in a total population is at present impossible to determine.

The pattern of inheritance is that of a simple Mendelian autosomal dominant (Figs. 7, 8, 9, 11, 12). Parental consanguinity has not been an impressive feature, but exceptions are described.[26] In a few instances, a recessive mode of inheritance seemed to be indicated by the presence of multiple affected members of one sibship with ostensibly normal parents. In only one of the pedigrees of this type which have come to my attention has it been practicable to do thorough investigations of parents and patients (Fig. 9). In the one kinship in which this was possible, I was forced to conclude that the mother was probably affected by a *forme fruste*. This woman had had at least three affected children by one man and one affected child by a second. The occurrence in one male and three females excluded the possibility of a sex-linked recessive trait. There was, therefore, no question but that each of the victims inherited the disease rather than getting it by *de novo* mutation and that the mother carries the gene. On examination, she was found to be 5 feet 8 inches tall, to be moderately long of limb without typical arachnodactyly, and to be myopic but free of ectopia lentis on careful ocular examination. This pedigree demonstrates how it is possible for the student of the full clinical and genetic picture to recognize cases which would be missed otherwise.

VOL. 2 1955

To my knowledge there has never been an opportunity to observe the effect of the gene in homozygous state; that is, the union of two affected persons has not been described. Skipping of generations has never been observed in any thoroughly studied pedigree.[68]

Partial submersion of the manifestations of this syndrome, depending apparently on the rest of the genetic milieu in which the mutant gene is operating, has been observed.[92] For instance, when the mutation occurs in unusually pyknic stock, the victim's habitus may be much less impressively unusual. No protection against ocular or aortic abnormality seems to be afforded thereby, however. The fact that in some families pronounced aortic and skeletal abnormalities occur without demonstrable abnormality of the lens structure seems to be further evidence of the operation of the genetic milieu on expression of the syndrome. Differences in the severity of the several components of the syndrome, including absence of some cardinal ones, is not inconsistent with the view that a single mutant gene is primarily responsible for the abnormality.

DIFFERENTIAL DIAGNOSIS

Given stigmata suggestive of the Marfan syndrome, one can be most confident of the diagnosis if ectopia lentis is present in the patient or if other members of the family are unequivocally affected (see Fig. 2). The possibility of the Marfan syndrome is encountered in many situations such as that of aortic regurgitation, otherwise unexplained, in an individual of asthenic and possibly dolichostenomelic habitus. Measurements taken alone are indicative but not completely conclusive. Measurements must be evaluated in the light of a rough

evaluation of the average habitus of the family of which the possibly affected individual is a member. In the first decade of life, comparison of upper and lower segment measurements and of arm span with height is of greater significance because of the relatively short extremities during this period.[154] (For normal values for these measurements during this period see references 40 and 181.) The lack of complete specificity of such measurements is indicated by the occurrence of excessively long extremities on an anthropologic basis in the Denker Negro[102] and on a pathologic basis in the eunuch.[13] The rule of thumb for identification of arachnodactyly—longest digit at least 50 per cent longer than the longest metacarpal—has proved to have both positive and negative error. In the Negro in particular, the Marfan syndrome is often suggested by skeletal proportions. A famous contemporary Negro basketball star is said to be 75½ inches tall, with an arm span of 84-86 inches. Sheldon[144] refers to this habitus as Nilotic dysplasia, since, according to him, inhabitants of the upper Nile area and their descendants display it most often. The Watussi tribe of Uganda is very tall.

A picture mimicking in some respects that of the Marfan syndrome can result from rh incompatibility and from intrauterine rubella infection. Ectopia lentis does not occur in these cases. However, deafness, ocular and cardiac defects, hypotonia, and even arachnodatyly may occur. The presence of some manifestation, such as anophthalmos, which is never encountered in the Marfan syndrome, is a point in favor of one of these other possibilities. Cases simulating Marfan's syndrome have occurred apparently as a result of the occurrence during early pregnancy of febrile illness of unspecified type[54] and of x-ray therapy.[152] (See Fig. 14.)

Institutions for mental defectives often list an unbelievably high percentage of patients with arachnodactyly. This should not be taken to indicate Marfan's syndrome in the majority of instances at any rate, since other evidence indicates that mental retardation is not an integral component of this syndrome and since it is clear that arachnodactyly is a nonspecific manifestation with many possible causes. The patient described by Benda,[17] for example, does not appear to have had a true Marfan syndrome.

Several of the individual components of the Marfan syndrome occur alone or as part of other heritable syndromes and on a genetic basis distinct from the Marfan syndrome. Pectus excavatum,[114,135,147] scoliosis,[55,133] myopia,[37,71] and hernia[44,176] are cases in point. Erdheim's cystic medial necrosis is almost certainly not a homogenesis entity from the etiologic standpoint (see below). Marfan's disease is but one cause, there being other genetic (e.g., Ehlers-Danlos syndrome) and possible acquired causes.

Several genetic varieties of ectopia lentis have been described.[16] One variety of isolated ectopia lentis is inherited as a simple Mendelian recessive.[51,167] I have observed[93] eight children of a first cousin marriage, of whom four had ectopia lentis and four had ateliotic dwarfism (a condition usually inherited as a recessive). Coincidence of the two anomalies occurred in two of the individuals. Another variety of ectopia lentis is inherited as a simple Mendelian dominant as in the Marfan syndrome but as part of the Weill-Marchesani syn-

drome.[92,100,175] The habitus of the victim of the Weill-Marchesani syndrome is diametrically opposite to that of the Marfan syndrome. The victim is brachymorphic, short of stature, with round head, pug nose, depressed nasal bridge, and short, pudgy hands and fingers.

In approximately 70 per cent of instances of congenital ectopia lentis, the anomaly occurs as a component of the Marfan syndrome. The skeletal manifestations of the Marfan syndrome may be so unconvincing in many cases that the presence of ectopia lentis in a patient with cardiovascular signs consistent with the Marfan syndrome should lead one to suspect the diagnosis even though the skeletal changes per se cannot be considered pathognomonic.

Muscular dystrophy was confused for Marfan's syndrome in the patient shown in Fig. 15,*A* and *B*. There were unusually pronounced spinal deformity and long fingers. The patient presented with bacterial endocarditis and aortic regurgitation—additional features suggesting the Marfan syndrome. Autopsy revealed no histologic evidence for this diagnosis but did show changes consistent with a rheumatic basis for the bacterial endocarditis. A brother, subsequently studied (Fig. 15,*C* and *D*) shows unequivocal evidence of muscular dystrophy. In children, the pronounced muscular hypotonia may result in a picture suggesting Oppenheim's amyotonia congenita or Werding-Hoffmann's muscular atrophy.

The relationship, if any, of the Marfan syndrome to "status dysraphicus" is obscure.[117] The latter condition is too ill-defined to make an analysis of relationship possible. We (see Fig. 3,*C*) and others have observed bent fifth fingers, so-called camptodactyly or clinodactyly,[70] and heterochromia iridis,[36] both manifestations which are said to be characteristic of status dysraphicus. Apparently identical clinodactyly is sometimes inherited as an isolated anomaly.[70]

PATHOLOGY

With the exception of the changes in the media of the great vessels and in the heart valves, no specific histologic abnormalities have been detected in this syndrome. In the media of the aorta, the most advanced changes are seen in cases of diffuse dilatation of the ascending aorta in which the process has gone on over several years' time and the patient succumbed to the effects of aortic regurgitation. In such cases, there are frequently early changes in the pulmonary artery. The early changes in the aorta are best demonstrated in those cases dying of dissecting aneurysm.

The advanced changes consist of fragmentation and sparsity of elastic fibers, irregular whorls of seemingly hypertrophied and perhaps hyperplastic smooth muscle, increase in collagenous tissue, pronounced increase in the vascularity of the media with wide dilatation of the vasa vasorum in both the adventitia and the media, cystic spaces occupied by metachromatically staining material. The net result is an aorta which is thicker (but weaker) than normal.

The early changes are those described by Erdheim[41] as cystic medial necrosis.[161] There are mild to moderate degeneration of elastic fiber elements and more or less striking cystic areas filled with metachromatically staining material.

VOL. 2 1955

The predominant involvement of the ascending aorta is not inconsistent with a generalized defect of some element of connective tissue, since it is the ascending portion of the aorta which bears the main brunt of hemodynamic stress. Reynolds[129] concluded that, with physiologic pulse pressures, it is only the ascending aorta which shows dilatation (i.e., increase in diameter) with each ventricular ejection. Other observers, while disagreeing with Reynolds' claim that virtually no expansile pulsation occurs beyond the arch, corroborate the finding that much greater expansion occurs in the ascending aorta (15 to 20 per cent increase over diastolic diameter in the ascending aorta, 5 per cent in the distal aorta). Engineers, textile scientists, and others concerned with testing the "strength of materials" are familiar with the fact that cyclical application of a stressing force results in structural disintegration much sooner than does steady application of the same force.

Another factor in the predominant localization in the ascending aorta may be implicit in Laplace's law (wall-tension = pressure × radius). Since both pressure and radius find their largest valves in the ascending aorta, the tension on the wall of that portion is greater than anywhere else in the vascular tree. In the case of aneurysm there is, by the same token, a vicious cycle or self-perpetuating action—the greater the radius, the greater the wall-tension, the greater the radius, and so on.

The predominant localization of the pathologic changes of Marfan's syndrome, of other varieties of Erdheim's cystic medial necrosis (see later), and of syphilis, in the ascending aorta, probably has its basis in the physical and hemodynamic considerations outlined above.

Changes similar to the early ones in the aorta are not uncommon in the main pulmonary artery. Occasionally the changes there are as advanced as are ever seen in the aorta.[166]

Minor changes in the heart valves in the form of marginal thickening or fibromyxomatous excrescenses have been described grossly in many of the autopsied cases,[136,146,162,175] including Salle's[136] case, the first autopsied. Histologically, one case[166] was found to show "numerous lacunas in the collagenous substance of the mitral valve that were filled with a homogeneous basophilic material." This lesion resembles closely that which occurs in the media of the aorta. Fig. 12,*F* represents the changes in the aortic valve in one of our cases. The pronounced sacculation and stretching of the aortic cusps is probably per se evidence of weakness of the connective tissue stroma of the valve. In the process of the stretching, breaks with fenestration of the cusp may occur.[168]

The pathologic studies of the eyes have not been very helpful from the fundamental standpoint. Hypoplasia of the dilator muscle of the iris provides explanation for the miosis and poor response to mydriatics.[79,137]

With the above exceptions (and, of course, the cystic disease of the lung), no histologic abnormalities have been detected. Specifically, peripheral arteries, joint capsules, ligaments, tendons, and periosteum have shown no abnormality, but studies in these areas are distressingly few.

THE BASIC DEFECT

In what element of connective tissue is the defect of the Marfan syndrome located? The histologic appearances in the aorta suggest that the primary defect may be in the elastic fiber. The pathogenic chain of events may be this[58]: The elastic fibers, constitutionally inadequate, undergo degeneration, particularly at the site of maximum hemodynamic stress, the ascending aorta. The smooth muscle elements, which normally have origin and insertion on the elastic lamellae, collapse together into disorganized whorls and undergo hyperplasia and hypertrophy. Reparative processes leave the media scarred. Secondary to the frantic hypertrophy of smooth muscle fibers and the scarring process, dilatation of the vasa vasorum occurs. (In 1933 Wolf[184] suggested that Erdheim's cystic medial necrosis might be a generalized weakness of elastic fibers. He demonstrated abnormalities in larger peripheral arteries and in the main pulmonary artery.)

What the suspensory ligament of the lens has in common with the media of the aorta is obscure. If known, the basic defect of this syndrome might be understood. It is possible to reconcile with a generalized elastic fiber defect many of the other manifestations: the lax joint capsules, the weak ligaments, especially those with large elastic fiber representation such as the ligamenta flava of the spine, the malformed elastic cartilages of the pinnae, and the deformity of the foot where elastic fibers are abundant in the ligaments.[155] But how is one to explain the most striking feature of this syndrome, dolichostenomelia, and the other dolichomorphic features? One gets the impression that the factor that is missing during morphogenesis and growth of bone in victims of this syndrome is a binding force which placed a rein on longitudinal growth. Whether it is elastic fiber as such or some element with the properties of the elastic fiber matters not at the moment. Is some such element missing from the ground material of the cartilaginous precursors of bone? Or is the location of the defect in the periosteum? The periosteum, attached as it is to the epiphyseal cartilage from which longitudinal growth occurs, may exercise control over longitudinal growth. Experiments of Ollier in 1867[109] and of others[80] since him, although not without flaw, suggest such to be the case: If a cuff of periosteum is removed from the circumference of a growing long bone, that bone will grow longer than its untampered counterpart. An inborn weakness of the periosteum might have a similar effect. The bony abnormality does not appear to be one of simple overgrowth since the excess is limited to longitudinal growth. The bones are abnormally small in cross section. Osteogenesis may be proceeding at a normal rate in the periosteum which slides along the diaphysis adding bone to the circumference; the diaphysis may not attain normal transverse dimensions because the periosteal bone is spread over a greater total area.*

*Lacroix[81] writes (p. 59) as follows: "A fibro-elastic membrane, the periosteum grows, while yielding to a traction imposed upon it, by stretching over its entire extent. Where only one zone of growth exists, as in the case of the long bones of the hand and foot, the periosteal sheath is attracted in only one direction: it is pulled in two opposite directions on the two sides of a 'neutral' zone in bones with two zones of growth. Since the diaphysis elongates only at the level of the growth cartilage, the periosteum during development slides along the bone surface at a rate and in a direction specific to each level." Later (p. 67), he writes: "Since the periosteum slides along the diaphysis which it encloses, the youngest trabeculae, those in formation at the moment of examination are not deposited at exactly the same level as those which the same zone of periosteum elaborated in the preceding days." The obliquity of the canals of the nutrient arteries has its origin in this phenomenon.

VOL. 2 1955

The precise element of connective tissue which is defective in Marfan's syndrome awaits identification. Nonetheless, it is possible to describe the behavior of the defect in considerable detail.

The production in rats of a somewhat analogous, but *acquired*, syndrome has been of great interest for obvious reasons. Kyphoscoliosis, hernia and aneurysm of the aorta (dissecting, diffuse, or saccular) can be produced in rats (Fig. 16) fed a toxic agent contained in the seed of *Lathyrus odoratus*.[28,120,122] The toxic material has been crystallized[38] and identified[138] as B (γL – glutamyl) aminopropionitrile ($HOOC-\underset{\underset{NH_2}{|}}{CH}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-NH-CH_2-CH_2-C\equiv N$).

B–aminopropionitrile will also cause skeletal changes and dissecting aneurysm of the aorta.[172] Gelatin and casein appear to afford partial protection against the effects of these toxins.[34] Whether the primary difficulty is in the elastic fibers or in the intermediate material is not clear.[10,32] The demonstration of increased mucopolysaccharide[32] is of interest in light of the metachromatically staining material seen in human cases of Erdheim's cystic medial necrosis including that caused by Marfan's syndrome (see below). Although the basic defect in this acquired syndrome is probably not the same as that in Marfan's syndrome, studies of this sort should be helpful in elucidating some of the many mysteries which surround dissecting aneurysm in particular[79] and disorders of connective tissue in general.

OTHER CONSIDERATIONS

There is, of course, no definitive treatment for this disorder. It should be noted that healing after surgical operations is normal. Herniorrhaphy, orthopedic procedures, and correction of pectus excavatum can be performed with success. (One patient went through a lienorenal shunt procedure for unrelated hepatic cirrhosis.[166]) Correction of pectus excavatum should probably be postponed until after puberty since an imperfect result may follow if there is still opportunity for excessive longitudinal growth of the ribs. The current philosophy in regard to ectopia lentis seems to favor performing lens extraction only if iritis or glaucoma develops. Hufnagel's plastic valve operation[73] was performed in a case of aortic regurgitation on this basis; because of the nature of this disease and of the operation currently practiced, its practicability here is very questionable. Evidence is presented elsewhere[95] that the Hufnagel operation produces widening of the pulse pressure (due both to increase in the systolic level and decrease in the diastolic level) proximal to the valve. This might well increase the strain on the already weakened ascending aorta and accelerate the process of dilatation or predispose further to dissection. In two recent cases (S.L., 293069; S.T., 691351) of idiopathic cystic medial necrosis of the aorta with diffuse dilatation of the ascending aorta and profound regurgitation, Dr. Henry T. Bahnson plicated the dilated aorta and surrounded the ascending aorta as far proximally as possible with a splinting slieve of synthetic fabric. A happy, although surprising, result of the procedure has been a pro-

nounced decrease in the aortic regurgitation as evidenced by diminution in the diastolic murmur and manifestations of left ventricular strain and by rise in diastolic pressure to almost normal levels. These cases are historic from another standpoint; it is the first time the diagnosis of Erdheim's cystic medial necrosis has been established histologically *in vitam*.

A point of medicolegal importance is the relationship of trauma to the development of various manifestations of the Marfan syndrome. The development of hernia, detachment of the retina,[94,140] dissecting aneurysm,[25,116,165] and total dislocation of the lenses may be intimately related to trauma as ap recipitating factor.

In connection with the relation of the Marfan syndrome to other diseases or special physiologic states, rheumatic fever, syphilis, hypertension, and pregnancy might be mentioned. The suggestion of Futcher and Southworth[53] that rheumatic fever may occur with increased incidence in these patients has not been confirmed by further observations. One patient (B.J., J.H.H. 699403) has had severe rheumatic fever and now has unequivocal rheumatic valvular heart disease, but, in general, the incidence is unimpressive. Syphilis and hypertension, if combined with the Marfan disease, might have particularly dire effects on the aorta. There is no careful autopsy documentation of the association, however. There is now convincing evidence of a strikingly increased incidence of dissecting aneurysm of the aorta in pregnancy.[102,141,143] Conceivably, this is related to the hormone "relaxin" and to the general relaxation of ligaments and other joint structures during pregnancy.[1,2,69,115,119,126,187]

VOL. 2 1955

Relation to Erdheim's Cystic Medial Necrosis[134].—Erdheim's disease is probably not a single entity from the etiologic standpoint. There are probably a number of possible "causes"—some genetic (like the Marfan syndrome), some acquired in nature. With the control of syphilis and rheumatic fever, cystic medial necrosis will assume increasing importance as a cause of aortic regurgitation. It must be kept in mind particularly when there is no history of syphilis, rheumatism, and bacterial endocarditis and must *not* be excluded from consideration on the grounds that there is no radiologic evidence of aortic dilatation. Unfortunately, the diagnosis of idiopathic Erdheim's disease (Erheim's disease without the Marfan syndrome) will for the time being need to be a diagnosis of exclusion.

The experience with Marfan's syndrome should prove very useful in the cases of idiopathic Erdheim's disease. In both, dissecting aneurysm or fusiform dilatation* or a combination can occur. In both, the ascending aorta is most severely affected. In both, the process seems to pursue an unrelenting progression to death from rupture of the aorta or from the effects of aortic regurgitation.

There is now convincing evidence[145] that the metabolic turnover rate in the elastic skeleton of the aorta is so low as to raise serious suspicions of complete

*Erdheim's disease is very familiar as a cause of dissecting aneurysm. That it can also cause diffuse or fusiform dilatation of the aorta is indicated by the surgically proved cases referred to above and by reports in the literature.[35,67,131,185,186,187] In some of these, insufficient clinical information is provided to permit exclusion of the Marfan syndrome.

metabolic inertia. The elastic structures of the aorta can be looked on as intended to outlive the rest of the organism. In certain unfortunate individuals, however, the elastica "gives out" prematurely. The result is Erdheim's cystic medial necrosis. Genetic inferiority is probably most frequently the basis. It has been described in brothers,[171] but the clinical information provided is too scant to permit exclusion of the Marfan syndrome. Erdheim's medial necrosis may be the cause of death in the first months of life or not until the ninth decade. Rupture of the aorta possible on a comparable basis is said to occur in horses and occurs in epidemic fashion in turkeys[97] where dietary factors may be responsible.

The treponemal immobilization test for syphilis has created a clinical problem in connection with patients with dilatation of the ascending aorta and aortic regurgitation, who often in the past would have been considered to be syphilitic in spite of negative serologic tests for syphilis of the conventional type. In coming years, cystic medial necrosis of the aorta, previously the exclusive property of the pathologists, will be discussed much more frequently in the clinical literature.

I am indebted to a large number of persons for assistance in accumulating the information presented here. Space does not permit mention of all of them. I would mention specifically Dr. Howard A. Naquin of the Wilmer Ophthalmological Institute. His contemporaneous investigations of ectopia lentis were helpful to the author's study of systemic aspects. Dr. Russell S. Fisher permitted me to examine the file of the Medical Examiner's Office of the City of Baltimore for cases of dissecting aneurysm of the aorta in young persons.

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VOL. 2 1955

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VOL. 2 1955

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VOL. 2 1955

SOME OBSERVATIONS ON 520 GOUTY PATIENTS

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ACUTE gout is a spectacular painful metabolic disorder. Since antiquity it has aroused the interest of physicians. The nature of the metabolic defect in gout is not yet apparent.

Elevation of serum uric acid and localized deposition of urates in the tissues are measurable characteristics of the disorder. Studies of the uric acid concentration in body fluids and estimation of the so-called "uric acid pool" have not lifted the veil from this metabolic mystery. It is indeed possible that these studies have merely been of "ashes" while the source of the "fire" has not been evident. (Fig. 1.)

Gout is a syndrome characterized clinically by recurrent attacks of painful acute arthritis, a tendency to localized urate deposition (*tophi* are its characteristic pathologic manifestation), eventual development of chronic polyarthritis, and possible renal insufficiency which may be terminal. Gout is seen predominantly in adult males and to a lesser extent in postmenopausal females whose serum uric acid concentration is elevated. The painful manifestations usually respond rapidly to colchicine, which if given in adequate dosage may serve as a diagnostic test.

Gout takes two principal forms[8]:

Primary gout is the usual type and is generally considered to be an hereditary disturbance of purine metabolism.

Secondary gout, which is much less frequently encountered, is a manifestation of pathologic physiology secondary to other diseases, chiefly those of hematopoiesis. Secondary gout has also been observed in patients subjected to prolonged administration of cortisone and hydrocortisone. Its occasional occurrence in the course of other disorders such as multiple myeloma may be only a chance correlation. The presence of acute gouty arthritis in long-standing uremia is probably explained by reduced renal function as a late manifestation of long-standing gout.

Since gout classically has been considered to be an acute painful involve-

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ment of the foot (*podagra*), many instances of gout involving other joints have been overlooked or misdiagnosed. The diagnosis of gout may often be overlooked in the early years of its development in the individual patient. At that time its manifestations may be both mild and intermittent. Since it is not the usual practice to determine serum uric acid on every patient complaining of muscular or articular discomfort, the true incidence of gout has been entirely conjectural. It should be emphasized that all patients complaining of nontraumatic musculoskeletal discomfort should have at least one serum uric acid determination.

In order to re-evaluate the clinical characteristics of gout and to place the disorder properly in present-day diagnostic and therapeutic procedures, the present study was devised.

By James Gillray (1757-1815)

Fig. 1.—"The Gout" by James Gillray (1757-1815). (Reproduced by permission of the Philadelphia Museum of Art.)

VOL. 2 1955

DIAGNOSIS

Gout should always be suspected, particularly in the male, in unexplained acute arthritis involving the metatarsophalangeal joint of the great toe (Fig. 2) accompanied by the characteristic suffused purple color of the skin. It is confirmed by the finding of a serum uric acid concentration above 6.0 mg. per 100 ml. and the specific response to treatment with colchicine which rapidly brings about subsidence of the acute symptoms.

It must be kept in mind, however, that the first complaint in the gouty patient may be from nonarticular manifestations, such as unexplained albumis nuria, eczema, elimination of an urate stone, as well as by abnormal localization of gout in joints of the spine where it is usually not suspected, advanced degenerative arthritis, and acute peritendinitis or bursitis of the shoulder. Due to the fact that the clinical manifestations of gout are numerous and involve almost every part of the body, the clinical criteria of diagnosis are of considerable importance.

A family history of gout, even though it is one generation removed, is significant. A family history of diabetes in the presence of acute arthritis may also be helpful since many gouty people give a history of diabetes among their immediate relatives. Approximately 20 per cent of relatives of gouty subjects will have hyperuricemia in the absence of a history of acute arthritis.[19] These hyperuricemic individuals should be considered as potentially gouty.

Fig. 2.—Acute gout showing marked distension and typical glistening skin over the great toe.

In the past history, there may be a story of acute painful joint distress which has subsided spontaneously within a few days or which has responded to colchicine. There is a frequent relationship of acute arthritic pain after prolonged standing or walking, long automobile or airplane rides (where the patient is forced to rest immobile for long periods of time), overindulgence in food or drink, following certain medications such as mercurial diuretics, liver extract, corticotropin, and following surgical procedures or immobilization in bed for medical illness.

With the present readily available diagnostic methods, in the absence of an elevated serum uric acid, the diagnosis of gout can only be made with certainty upon demonstration of a tophus containing the characteristic urate crystals. If the patient has taken salicylates or other medication promoting uricosuria, the uric acid determination may be normal and must be repeated several times

in the absence of medication for certainty of diagnosis. Of course, gout may be strongly suspected in individuals who have the clinical characteristics described above in the absence of elevated serum uric acid. In such instances it is advantageous to employ a provocative test if the diagnosis is of great importance. This can be accomplished by administration of crude liver extract intramuscularly, high-fat diet, or by feeding large amounts of asparagus, high-purine diet, and possibly by drinking large quantities of red wine or beer. If an acute exacerbation follows the use of one or several of these procedures, the serum uric acid will probably be elevated during the acute attack. During natural fluctuations of the disease process, the uric acid might occasionally be within the normal range. In the majority of cases, the uric acid is above 6.0

Fig. 3.—Radiograph of hand and wrist in chronic tophaceous gout. The third finger has been amputated because of a massive tophus. Multiple "punched-out" areas are characteristic.

VOL. 2 1955

mg. per 100 ml. of serum in the absence of medication with uricosuric agents; a slightly lower value, 5.5 mg. per cent, may be applicable in the female.

In the initial examination it is advisable for the patient suspected of gout to have x-ray studies of the feet and ankles in addition to other joints which might, at the moment, be affected. The characteristic "punched-out area" is strongly suggestive of gout (Fig. 3). These punched-out areas do not have an area of sclerosis surrounding them as do cystic areas in osteoarthritis or rheumatoid arthritis, and, occasionally, the punched-out area actually erodes into a joint. A characteristic bony lesion of gout progresses to complete bone resorption followed by expansion of the cortex which results in a remaining thin shell of bone around the outer aspect of the lesion. Tophi are opaque only in those instances where there has been a secondary deposition of calcium (Fig. 4).

The differential diagnosis of primary gout and rheumatoid arthritis, based upon our experience with 504 patients, is as follows:

DIFFERENTIAL DIAGNOSIS

	Primary Gout	*Rheumatoid Arthritis*
Sex	Predominantly in males; uncommon in female before menopause; rare in males before puberty	More frequent in female; may exist in children
Body Type	Sthenic, often obese	Thin, asthenic
Heredity	Often positive	Usually negative
Energy	Often hyperactive	Usually exhausted, hypoactive
Color	Ruddy	Pallor
Tophi	13 per cent in males and 3.8 per cent in females	None
Olecranon bursitis	Frequent	Unusual
Odor	Characteristic	None characteristic
Subcutaneous nodules	None	In 5 per cent
Nails	Often show chalklike deposits	No characteristic change
Pain	Excruciating in exacerbation; little relieved by rest	Usually mild and relieved by rest
Attack frequency	Increase with age; usually free of symptoms between attacks	Slow onset frequently; tendency to early recurrence and chronicity
Number of joints involved	Usually monarticular	Usually multiple
Renal changes	Renal impairment and calculi may be observed	Rare
Osteoporosis, generalized	Rare	Usually present
Ankylosis	Rare	Not uncommon
Muscle atrophy	Usually absent; strong grip	Usually present, may be marked; "stiffness" frequent; weak grip
Anemia	Tendency to plethora	Often present
Sedimentation rate	Elevated in acute attacks	Usually elevated
Colchicine (in adequate dosage)	Prompt relief of acute symptoms—especially in early cases	No effect
Serum uric acid	Usually above 6.0 mg. per 100 ml. for males and 5.5 mg. for females	Usually normal except during prolonged cortisone administration

CLINICAL OBSERVATIONS

Although gout has been described as a disorder predominantly of the male, we have included in this report observations on primary gout in 373 males and 131 females (Table I). There were no Negroes in this study. All were Caucasians except 3 Chinese, 4 Filipinos, and 3 Japanese. With few exceptions the patients resided in the mild, temperate climate of Northern California, principally in the counties surrounding the Bay of San Francisco. No clinic patients were included. In fact, the incidence of gout in part-pay clinics in this area is not large.

Fig. 4.—Calcified tophi in olecranon bursa.

In preparation of the tables of data* in these studies we chose to classify the patients into two categories, viz., "acute intermittent" and "chronic." The "acute intermittent" category includes those whose attacks of gout were of sudden onset and short duration and who enjoyed asymptomatic intervals of variable duration. The "chronic" designation was reserved for those who had musculoskeletal discomfort most of the time unless medicated appropriately. In the latter group were the chronic gouty arthritics, among whom were those with visible tophi. The "chronic" patients, of course, were subject to acute exacerbations which resembled in every way those of the "acute intermittent" group.

Seventeen per cent of the males were less than 40 years of age (Table I) while only 9 per cent of the females were that young. These 12 younger females

*The clinical and laboratory data were assembled on punched cards employing 204 classifications to facilitate their optimum utilization.

VOL. 2 1955

TABLE I. SEX AND AGE DISTRIBUTION OF PRIMARY GOUT IN 504 PATIENTS

DECADE	MALE		FEMALE		TOTAL
	ACUTE INTERMITTENT	CHRONIC	ACUTE INTERMITTENT	CHRONIC	
2	3	0	0	0	3
3	6	6	1	4	17
4	24	26	4	3	57
5	49	39	11	16	115
6	49	57	25	18	149
7	31	36	10	21	98
8	15	27	7	6	55
9	1	3	3	2	9
10	0	1	0	0	1
Subtotal	178	195	61	70	504
Total	373 (74%)		131 (26%)		504 (100%)

were still menstruating—9 regularly and 3 irregularly. There were no instances of "surgical" or premature menopause among them. At the other end of the age scale, 12.6 per cent of the males and 13.7 per cent of the females were over 70 years of age. After age 50 chronic gout was more common than acute intermittent gout in the males. In the females in the same age group acute and chronic categories were almost equal.

TABLE II. DURATION OF PRIMARY GOUT IN 504 PATIENTS
(Prior to the Present Evaluation)

YEARS	MALE		FEMALE		TOTAL
	ACUTE INTERMITTENT	CHRONIC	ACUTE INTERMITTENT	CHRONIC	
0–1	91	53	32	18	194
1–5	36	45	8	20	109
5–10	32	30	13	7	82
10–15	5	17	3	8	33
15–20	9	20	0	8	37
20+	5	30	5	9	49
Total	178	195	61	70	504

As nearly as could be determined the duration of symptomatic gout was estimated according to the clinical histories. Table II includes the distribution of patients according to the interval from the first symptoms of gout until their first examination by us. Twenty-three per cent of the males had had symptoms of gout, either acute or chronic, for more than ten years. Twenty-four per cent of the females had had symptomatic gout for more than ten years prior to our examination of them.

The presence of visible tophi (Fig. 5,*A* and *B*) among the gouty has been a subject of considerable interest. There is no satisfactory explanation for the rate of growth of tophi. The incidence of visible tophi in any series of gout patients probably depends upon several factors. It is conceivable that if the gouty patients are selected from the population of a large general clinic, many early and atypical instances of gout will be overlooked. Such a situation would produce a series with relatively frequent visible tophi. On the other hand, if one evaluates the serum uric acid on every patient with painful musculoskeletal disorders, many early and unsuspected instances of gout will be revealed. In the latter situation one would not expect to see as many tophi, since it has generally been accepted that the number of tophi observed is greater as the duration of the disease increases and as the patients age. Our data are drawn from such a situation (Table III); and we have observed visible tophi in 13 per cent of males and 3.8 per cent of females. In our experience the number of tophi appears to increase as the patients become older, and 60 per cent of the visible tophi in our series were observed in patients whose gout had been symptomatic for more than ten years. On the other hand, in one of the females who had a plastic surgical procedure performed on the first metatarsophalangeal articulation a tophus appeared in the extensor tendon sheath proximal to the joint postoperatively, and at the end of two months it was 1 cm. in diameter. When removed surgically this rapidly growing tophus could not be distinguished from other tophi which had been present for many years. In view of this observation we are forced to believe that factors other than age of the patient and duration of symptoms may be responsible for local deposition of urate crystals.

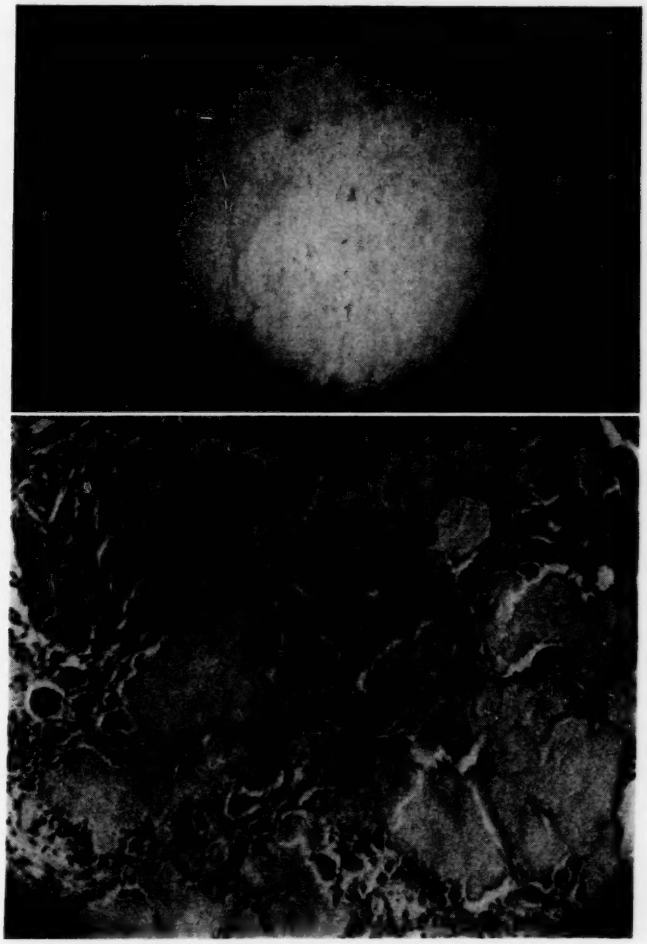
VOL. 2 1955

TABLE III. VISIBLE TOPHI IN PRIMARY GOUT
(54 Instances Among 504 Patients)

DECADES	MALES	DURATION OF GOUT (YEARS)							
		0–1	1–5	5–10	10–15	15–20	20–25	25–30	30+
4	2	1				1			
5	9	2	2	1	3	1			
6	18	3	1	3	1	6	3	1	
7	13	1	1	3	1	2	1	2	2
8	7		1	2		1			3
	49	7	5	9	5	11	4	3	5
	Females								
6	1					1			
7	2			1			1		
8	2								2
	5			1		1	1		2
Total: Male and Female	54	7	5	10	5	12	5	3	7

The initial determination of serum uric acid is often done after the patient has received medication causing increased urinary excretion of urates. Thus, among the *initial* uric acid determinations of a large group of gouty individuals one might expect to find a considerable number in the normal range. Fig. 6 illustrates the range of initial *serum* uric acid levels in acute and chronic primary

A.



B.

Fig. 5.—*A*, Tophaceous mass excised from tendon sheath on dorsum of foot. *B*, Microscopic detail of tophaceous mass shown above.

gout. These uric acid determinations were made by the colorimetric method of Brown.[4] Among the males 15.5 per cent had serum uric acid levels below 5.5 mg. per 100 ml., and 27.5 per cent were below 6.0 mg. per 100 ml. The trend of females to have lower serum uric acid levels is shown by the presence of 27.1 per cent below 5.5 mg. and 41 per cent below 6.0 mg. per 100 ml.

As individual patients are followed for several years, it is apparent that with rare exceptions all of them show high serum uric acid levels sooner or later during unmedicated intervals. When the diagnosis is in question, determination of the twenty-four-hour urinary excretion of uric acid is often helpful. With the use of uricosuric agents (e.g., probenecid, phenylbutazone, corticotropin, or salicylates) the amount of uric acid excreted by the gouty far exceeds that of the nongouty. In such instances it is well to maintain urinary alkalinity to prevent crystallization of the relatively insoluble uric acid in the urinary tract. We have, for example, observed a 36-year-old woman from a gouty family increase her twenty-four-hour urinary output of uric acid from 0.79 Gm. to 8.5 and 8.9 Gm. under the influence of probenecid for two days. Concurrently her serum uric acid decreased from 5.5 to 2.8 mg. per 100 ml. During the same three-day interval the daily excretion of creatinine did not vary appreciably.

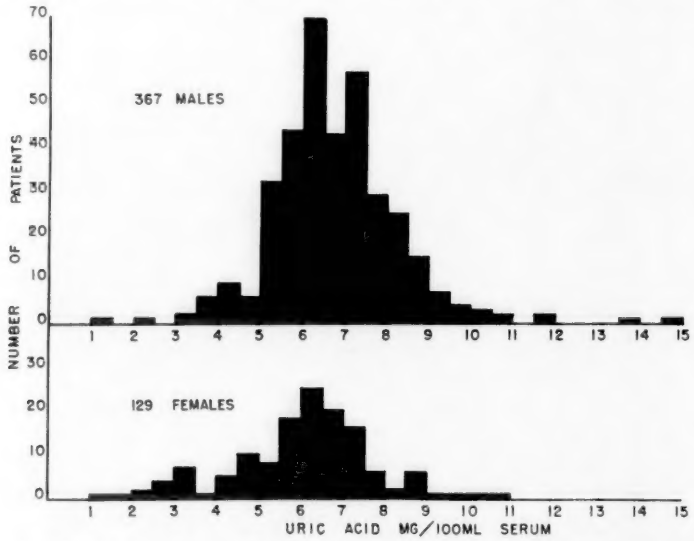


Fig. 6.—Range of initial serum uric acid levels in acute and chronic primary gout. These patients had almost always received variable amounts of uricosuric medication prior to the initial examination (see text).

In view of the above observations we have frequently made multiple observations of serum uric acid on individual patients, and we emphasize that ruling out gout on the basis of a single determination is unwarranted.

A method employing uricase[5] for the specific enzymatic estimation of serum uric acid was applied to 100 samples of serum from an assortment of gouty and nongouty patients. At the same time the serum uric acid was determined by the conventional colorimetric method on an aliquot of each sample. The results of this comparison are presented in Fig. 7. Each pair of results is indicated by a single point, the abscissa showing the value found by the uricase method and the ordinate the difference between the value found by the colorimetric and uricase methods. All tests in which the colorimetric method gave a higher value are represented by a dot above the zero-axis, and all tests in which the colori-

VOL. 2 1955

metric method gave a lower value than the uricase method are illustrated by a dot below the zero axis. An inspection of the figure shows 50 points above, 48 below, and 2 on the zero-axis. Above 6 mg. per 100 ml. there are 8 points above the axis and 18 below, indicating that as the serum uric acid level rises, the uricase method tends to give higher values. Conversely as the level of serum uric acid, below 6 mg. per 100 ml., decreases toward zero, there are more points above the axis, indicating that in this range the conventional method yields higher values. A further analysis of the data (to be reported in detail elsewhere[15]) reveals that in the area below 4 mg. per 100 ml. the conventional method gives higher values in females than in males. This suggests that females may possess a greater concentration of some unidentified chromatogenic substance other than uric acid.

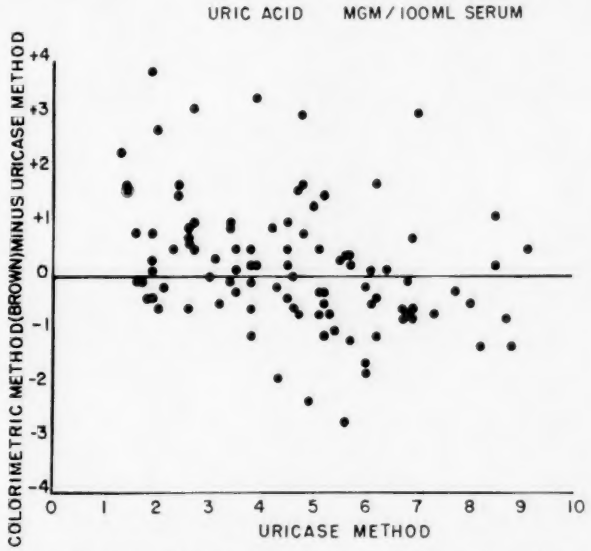


Fig. 7.—A comparison of the spread in 100 serum uric acid determinations done in duplicate by the colorimetric (Brown) and the enzymatic (uricase) methods. This group included normal, gouty, and patients with a variety of rheumatic disorders.

When one evaluates the considerably greater technical difficulty in performing the enzymatic determination, the unavailability in clinical laboratories of spectrophotometers for measurements in ultraviolet range, the relative ease of performing serial serum uric acid determinations by the colorimetric method, and the fact that the measurement of uric acid has not revealed the nature of the metabolic defect in gout, the colorimetric method will doubtless remain in general use. In the proper performance of the colorimetric method the freshness of the reagents is of considerable importance.

COINCIDENCE OF OTHER PAINFUL MUSCULOSKELETAL DISORDERS

The coincidence of other painful musculoskeletal disorders with primary gout was determined, since it was apparent that frequently patients presented complex problems which could not be solved entirely by treatment of the gout.

In Table IV the per cent coincidence of these disorders in our patients is shown. Osteoarthritis (degenerative joint disease), bursitis, and peritendinitis were most commonly encountered. The 34 per cent incidence of osteoarthritis in gouty females represented the most common coincidence of two disorders. One wonders whether the 5.4 and 7.6 per cent coincidence of rheumatoid arthritis and gout for males and females, respectively, is not more than simple chance correlation. The answer is, however, not available from the data under consideration. On the other hand, the 4.8 and 3.0 per cent coincidence of ankylosing spondylitis and gout for males and females, respectively, suggests more than chance correlation because ankylosing spondylitis is much less common than rheumatoid arthritis where the coincidence figures with gout were only slightly greater. It is perhaps of interest that the hereditary tendency in ankylosing spondylitis and gout is also greater than is generally recognized in rheumatoid arthritis.

VOL. 2 1955

TABLE IV. COINCIDENCE OF MUSCULOSKELETAL DISORDERS WITH PRIMARY GOUT

DISORDERS	373 MALES	131 FEMALES
Ankylosing spondylitis	18 (4.8%)	4 (3.0%)
Rheumatoid arthritis	20 (5.4%)	10 (7.6%)
Psoriasis with arthritis	3 (0.8%)	2 (1.5%)
Osteoarthritis	68 (18.2%)	45 (34.4%)
Bursitis, Peritendinitis of shoulder	39 (10.5%)	20 (15.3%)
Malum coxae senilis	16 (4.3%)	6 (4.5%)
Panniculitis	3 (0.8%)	5 (3.8%)
Disc herniation	20 (5.4%)	2 (1.5%)
Osteoporosis	4 (1.1%)	5 (3.8%)
Reiter's syndrome	2 (0.5%)	0
Paget's disease	5 (1.3%)	0

ASSOCIATED DISORDERS

In studying the association of various diseases, one must remember that, if the disorder of primary interest tends to become more severe with advancing age of the individual and more prevalent in older age groups, the natural association with disorders subject to the same trends is not surprising. Such associations would then be of little etiologic interest. Negative associations might, in fact, be of greater importance.

The coincidence of a variety of diseases with primary gout is presented in Table V. Obesity was present in half of both males and females, while hypertension was present in one-fourth of males and one-third of females. Sixty-nine per cent of hypertensive males and 57 per cent of hypertensive females were also classed as obese. There were only four gouty males and one female whose systolic pressure was usually below 100 mg. Hg. Thyroid deficiency was observed in one-fifth of males and about one-third of females. Cardiac disorders (myocardial infarction, valvular heart disease, and cardiac decompensation) appeared in 10.7 per cent of males and 1.5 per cent of females. We realize that such figures might be misleading due to difference in numbers and ages of males and females under consideration. Hay fever and urticaria appeared to be more common among females, while asthma was about equally prevalent among males

TABLE V. COINCIDENCE OF A VARIETY OF DISEASES WITH PRIMARY GOUT

DISEASES	373 MALES (PER CENT)	131 FEMALES (PER CENT)
Hypertension	25.7	35.8
Cardiac disorders*	10.7	1.5
Obesity	54.6	51.9
Hypothyroidism	18.7	29.7
Underweight	8.0	16.0
Prostate disorders*	11.2	——
Diabetes	3.4	0.7
Psoriasis	3.2	6.1
Other skin disorders	8.0	9.1
Ocular disease	7.5	9.1
Gastrointestinal*	13.9	17.5
Alcoholism	6.1	3.0
Renal stone	5.3	0.7
Renal insufficiency	4.8	3.8
Plumbism	0.2	——
Cerebrovascular accident	1.3	——
Hay fever	12.6	20.6
Asthma	5.8	4.5
Urticaria	5.0	10.6

*More fully described in text.

and females. It was also of interest that the per cent of underweight women was greater than that of men in this disorder, which may be related in some way to fat metabolism.

Diseases which have in the past been considered prevalent among the gouty were not prominent in our data. A history of lead poisoning, for example, was obtained in only one instance. Renal stone was noted in only 5.3 per cent of males and in less than 1 per cent of females. Renal insufficiency, usually emphasized in clinical descriptions of gout, was infrequent in this group, perhaps indicating earlier case finding. Ocular disorders (other than refractive errors) were seemingly common, being present in about one-twelfth of patients and including cataract, uveitis, chorioretinitis, and retinal detachment.

Alcoholism, which in the past has been strongly associated with gout in the literature, was found to be relatively uncommon in our patients. This was surprising in a region where wine drinking is neither uncommon nor expensive. To our knowledge there were few total abstainers in the group, yet alcoholism was a problem in only 6.1 per cent of men and 3.0 per cent of women. Although diabetes is frequent among the relatives of the gouty, the incidence of the disorder in this group was small. "Gastrointestinal disorders" included peptic ulcer, cholelithiasis, nervous indigestion, and diverticulitis, so that its per cent coincidence was apparently not remarkable.

CAUSE OF DEATH IN PRIMARY GOUT

Eighteen patients expired with a variety of disorders (see Table VI). Myocardial infarct was the cause of death in 61 per cent of these. Renal failure was responsible for the death of only 2 of the 18 (11 per cent). Ungerleider[21] in a recent study of actuarial data of life insurance revealed no increased mortality in gout as compared with the general population.

TABLE VI. CAUSE OF DEATH IN PRIMARY GOUT
(Number of Patients)

CAUSE	MALES	FEMALES	TOTAL
Myocardial infarct	10	1	11
Cerebrovascular accident	0	1	1
Pulmonary embolism	0	1	1
Cardiac decompensation	0	1	1
Carcinoma	1	1	2
Renal failure	2	0	2
Totals	13	5	18

SECONDARY GOUT

In addition to the 504 patients with primary gout, 16 patients with secondary gout were included in this study (Table VII). Nine of the 16 presented the picture of acute intermittent gout superimposed upon rheumatoid arthritis which was under prolonged treatment with cortisone acetate, a situation which has been described by Batterman and Traeger.[2] The occurrence of acute gout secondary to other disorders, particularly those of hematopoiesis, is of interest principally in that the painful arthritis may be the first manifestation of the underlying disorder. Treatment of the acute gouty arthritis seen in this group is in the usual manner employed in primary gout as described below.

TABLE VII. SEX DISTRIBUTION OF SECONDARY GOUT IN 16 PATIENTS

PRIMARY DISORDER	MALES	FEMALES	TOTAL
"Steroid"*	5	4	9
Leukemia	3	0	3
Hodgkin's disease	1	1	2
Multiple myeloma	1	0	1
Pernicious anemia	0	1	1
Total	10	6	16

*Prolonged oral administration of cortisone and/or hydrocortisone acetate in rheumatoid arthritis.

UNUSUAL LABORATORY FINDINGS

*"Atherogenic Indices."**—In view of the long-recognized association of gout and obesity as well as the well-established clinical impression that fatty foods should be interdicted in gout, it was thought interesting to determine the "atherogenic indices"[7] of an unselected group of patients with gout.

*The atherogenic index[7] is an index of coronary atherogenicity and

$$\text{A. I.} = \frac{1.0\ (\text{Standard } S_f0 - 12) + 1.75\ (\text{Standard } S_f12 - 400)}{10}$$

where (Standard $S_f0 - 12$) and (Standard $S_f12 - 400$) lipoproteins are measured in mg. per 100 ml. serum. The "Standard" indicates that a refined procedure which takes into account the self-slowing of lipoproteins with increasing concentration has been used. One "S_f unit" = a flotation rate of 1 x 10^{-13} cm. per sec. per dyne per Gm. at 26° C.

VOL. 2 1955

Table VIII summarizes these observations. Nine patients with tophaceous gout showed an average "atherogenic index" of 108. The "atherogenic indices" in 6 instances of gout without observable tophi averaged 107.5. An upper normal "atherogenic index" in this distribution of ages would be less than 80. The

TABLE VIII. "ATHEROGENIC INDICES"[7] OF PATIENTS WITH PRIMARY GOUT

PATIENT	AGE (YR.)	SEX	APPRAISAL OF OBESITY*	SERUM URIC ACID (MG./100 ML.)	MEDICATION	OTHER DISEASES	"ATHEROGENIC INDEX"
				I. Tophaceous Gout			
1	73	M	+ + +	9.4	Heparin (I.M.) Colchicine (I.V.)	Myocardial infarct, old; angina pectoris, severe; uremia, moderate, chronic	88
2	65	M	+ + +	8.5	Colchicine (oral) Raudixin ®	Myocardial infacrct, old; cerebral infarct, recent	125
3	53	M	+ + +	10.0	Phenylbutazone, oral	None	102
4	54	M	+ + +	9.0	Colchicine, oral	Myocardial infarct (expired)	116
5	69	M	+ + +	8.3	Colchicine, oral Phenylbutazone, oral	Psoriasis	120
6	53	M	+ + +	8.5	None	None	142
7	71	M	Normal	9.1	Colchicine, oral	Myocardial infarct; renal stones; angina pectoris	92
8	66	F	Normal	8.9	Phenylbutazone, oral	Hypertension; carcinoma, nipple	95
9	47	M	+ +	9.4	Oral and I.M. Phenylbutazone	Hypertension; renal stone	93
				II. Acute Intermittent Gout			
1	45	M	+ + +	8.0	Colchichine, oral; Phenylbutazone, oral	Mental depression, episodic	111
2	56	F	+ + +	6.8	Colchicine, oral; salicylates	Hypertension	127
3	43	M	+ + +	8.0	None	Renal stones	100
4	52	M	Normal	7.8	None	None	99
5	71	M	Normal	7.8	Colchicine, oral; Phenylbutazone, oral	Prostatism; cataract	83
6	72	M	Normal	12.0	None	Hypertension; uremia, chronic, mild	124

*A clinical estimate (from + to ++++) supplementary to usual height and weight measurements.

conclusion apparent from this small study is that individuals with gout have a marked tendency to high "atherogenic indices." The possible significance of these observations is the subject of further study.[17]

Since Örström and Örström[18] in 1950 reported markedly diminished serum glutamine in gout, we have attempted to confirm their observation. Thus far, using methods of microbiologic assay,[16] we have been unable to find significantly lower serum glutamine in patients with gout.

Glutathione.—In a previous study we have reported the variations in blood glutathione* in rheumatoid arthritis, ankylosing spondylitis, and gout.[9] In Table IX the ratio of the reduced to the total blood glutathione in these disorders is presented. Generally the ratio was higher in the gouty than in the other patients and was close to normal. These studies were initiated since alterations in levels of blood glutathione have followed administration of corticotropin, which is used therapeutically in acute gout. As a diagnostic test the determination of blood glutathione is of no help in gout.

TABLE IX. RATIO OF REDUCED TO TOTAL GLUTATHIONE IN BLOOD
(GSH::GSSG in mg./100 ml.)

Normals	(9)	.78				
	Acute		*Chronic*		*Quiescent*	
Gout	(6)	.73	(18)	.76	(6)	.80
Rheumatoid arthritis	(16)	.62	(27)	.76	(5)	.76
Ankylosing spondylitis	(5)	.60	(13)	.69		

TREATMENT

Effective treatment of gout embraces several features, i.e., control of the acute exacerbations, treatment of chronic gouty arthritis, reduction in size of tophi, and prevention of recurrent acute exacerbations.

Acute Attack.—During the violent pain of the acute attack, local measures are of little value. Colchicine administered orally in adequate dosage is effective in a majority of cases but produces cramps and diarrhea in many patients.

Administered intravenously, colchicine is quite effective in a period of several hours. We have observed rapid favorable action of colchicine when given in a single dose of 3 mg. in 5 ml. physiologic saline intravenously. Occasionally the use of colchicine intravenously is followed by severe thrombophlebitis which persists for three weeks and which usually extends distally as well as proximally from the site of injection.

The intravenous use of demecolcine (Colcemide) has likewise proved effective in 19 of 20 acute exacerbations of gout.[12] Of the 20 patients, 15 enjoyed complete remission within forty-eight hours after the administration of 1 to 4 mg. demecolcine. Four other subjects were afforded partial amelioration of signs and symptoms. There were no instances of phlebitis following its use in this small group.

*The idiometric method of Woodward and Fry[22] was used in the estimation of the blood glutathione.

VOL. 2 1955

When colchicine is employed orally in the treatment of an acute attack, it should be administered in effective dosage in order to obtain optimum effect. The usual method is to administer 0.5 mg. every hour for 6 or 8 doses or until acute gastrointestinal distress necessitates its discontinuance. It is important that the hourly administration be continued even at night if the course of medication is begun late in the day. Following the onset of cramps and diarrhea, the acute joint manifestations usually begin to subside. In such individuals it is probably wise to continue administration of colchicine, 0.5 mg. 3 or 4 times daily for a week. Occasionally it may be helpful to provide patients with camphorated tincture of opium for amelioration of the intestinal cramps which are often almost as bothersome as the gout itself. If it is necessary to give a second full course of colchicine, an interval of at least forty-eight hours should be provided to prevent excessive toxicity.

The use of salicylates during acute exacerbations has not been effective in our hands, and we have long since abandoned their use for such a purpose. We realize, however, that it is quite possible that prompt ingestion of large amounts of salicylates may abort many attacks of gout and that those which come to the attention of the physician are possibly the more severe attacks which have defied self-medication.

Phenylbutazone (Butazolidin), a pyrazole compound, administered orally and intramuscularly is usually quite effective in acute gout.[10,11,13,14] Often within a few hours of oral administration and occasionally within a few minutes of intramuscular injection the joint pain and swelling begin to subside. The usual oral dosage for acute gout is 200 mg. 2 to 3 times daily until the acute symptoms have abated, and thereafter 100 mg. 2 or 3 times daily for a week. Intramuscularly, 600 mg. daily for 1 or 2 days, followed by oral medication, is usually sufficient. The use of 250 mg. rectal suppositories is also possible if oral administration is not desirable.

Corticotropin may likewise be employed in acute gout, often with quite dramatic success. It may be given intramuscularly in a gel, 60 to 80 units daily, until the desired effect is produced and then for 3 or 4 days in progessively reduced daily dosage. It may be desirable to give colchicine, 0.5 mg. orally 2 or 3 times daily, during this procedure to prevent the sudden rebound of acute gout after cessation of corticotropin therapy. Corticotropin may preferably be given, when convenient, by slow intravenous drip during a 6- to 8-hour period, employing 10 to 25 units daily. We have reserved such medication for the unusual instance of acute gout not amenable to other simpler and less costly measures or for those sensitive to other medication.

Cortisone, hydrocortisone, and metacortandracin have been poorly tolerated when given orally in acute gout. There has been a tendency for exacerbation after initial subsidence of the acute attack.

Hydrocortisone acetate or tertiary-butyl-acetate injected locally into acutely inflamed gouty articulations is often rewarding as an adjunct measure. Depending upon the size of the joint involved, 10 to 50 mg. of the suspension may be employed.

Probenecid (Benemid), a sulfonamide, has no place in the treatment of acute gouty arthritis.

Chronic Gout.—The treatment of chronic gout includes control of acute exacerbations which occur superimposed on chronic gouty arthritis, treatment of tophi, and prevention of recurrent acute gouty arthritis.

In management of the acute flare-up in chronic gout the same general measures as in acute intermittent gout are applicable.

Formerly, treatment of chronic gouty arthritis was by daily use of salicylates, 0.6 Gm. 3 or 4 times daily, plus colchicine 0.5 mg. once or twice daily, together with avoidance of certain foods alleged to cause the disorder to flare up. Ideally the control of obesity should also be a major part of the treatment in chronic gout.

Complete control of urate formation by dietary regulation is impossible, since there is evidence in isotope studies that purines are synthesized in the human from the simplest carbon derivatives of carbohydrate, fat, and from nitrogen derived from protein sources. In addition, in outlining a regimen for gouty patients, consideration of a balanced diet with adequate amount of protein, iron, and vitamins should be observed since oftentimes gouty victims who in the past were treated with low-protein diets lacked energy and probably were in negative nitrogen balance. In general, it has been our impression that changing chronic gouty patients over from the "old-style" diet with high-carbohydrate and low-protein intake to a relatively high-protein, low-carbohydrate, low-purine, low-fat diet resulted in a desirable decrease in obesity and a general increase in vigor. Foods high in purine content are avoided, obviously to relieve the already overburdened mechanism for the disposition of such substances. Low-fat intake presumably prevents the retention of uric acid which is observed in the presence of high-fat intake. Vigorous reducing diets have the effect of causing the patient to "burn" his own fat too rapidly, thus impeding urate excretion.

The use of liberal quantities of fluid is desirable and possibly alkalinization of the urine should be encouraged to prevent precipitation of urate crystals.

As a result of our empirical observations and those of others we encourage avoidance of the following:

1. Liver, sweetbreads, brains, kidney, anchovies, and sardines.
2. All meat extracts, gravies, and broths.
3. Asparagus, cauliflower, broccoli, mushrooms, dried beans (lima, kidney, navy), lentils, peas, and spinach.
4. Chocolate, cocoa, and cola beverages.
5. Beer, ale, and red wine. Scotch whiskey may usually be tolerated.
6. Whole grain cereals and oatmeals (any other cereal may be eaten). Use white bread or soya bean bread.
7. Carbonated beverages.
8. Fresh peaches, apricots, and grapes.

VOL. 2 1955

In recent years with the use of phenylbutazone and probenecid the treatment of chronic gout has become simpler and more effective. Phenylbutazone in a daily oral dose of 100 to 300 mg. is effective in prevention of acute exacerbations as well as alleviation of the pain and swelling of the chronic gouty arthritis. It is now generally accepted that phenylbutazone in moderate to high dosage is an uricosuric agent.[23,24] Its effectiveness in controlling the symptoms of acute and chronic gout as well as the prevention of acute exacerbations is usually achieved in a dosage range below that necessary to induce increased uricosuria. When the warning signs of an acute attack appear, increase of the daily ration to 600 mg. for 1 or 2 days prevents progression of the acute flare-up.

Probenecid is the most effective uricosuric substance available at the moment. Its use for reduction of size of tophi has been effective.[1,3] It has no value in treatment of the acute attack; in fact, its use may induce acute exacerbations, a property which could be of value as a provocative test in doubtful cases. Use of 1 to 2 Gm. daily in patients without impaired renal function and in the absence of salicylates (which block its action) permits reduction in size of tophi. Since uric acid precipitates in acid urine, daily testing of the urine with appropriate "indicator" papers may be helpful in regulating use of the drug.

Surgical excision of tophi may be performed when possible if their size and location is such that the function of other structures is impaired.

RESULTS OF TREATMENT

In evaluation of results of treatment, three categories were designated. A "good" result indicated subsidence of symptoms within forty-eight hours. "Fair" result described a complete disappearance of symptoms of gout in from 2 to 7 days. "Poor" indicated little or no amelioration of symptoms following treatment. In Table X are summarized the responses to treatment in this series of patients.

The use of phenylbutazone has been more effective in treatment of both acute and chronic arthritis of gout than has any other agent. A comparison with colchicine is interesting. Ninety-one per cent of those treated with phenylbutazone experienced a "good" or "fair" response while with colchicine the comparable response was only 80 per cent. Perhaps of greater general interest is the observation of 20 per cent poor responses to oral colchicine. While the acute arthritis of gout is the only type of arthritis which responds to colchicine, it must be remembered that colchicine administered orally is not always effective during the acute phase of the arthritis. Phenylbutazone, which is more often effective in the acute arthritis of gout, is also effective in other forms of rheumatic disease; thus it cannot be classed as a "specific" for gout. Among the 378 patients treated with phenylbutazone were 32 treated with Irgapyrin (a mixture of equal parts of phenylbutazone and aminopyrin). They were included with the others since aminopyrin itself had not been a recognized effective antigout medication.

Considering males and females together and comparing phenylbutazone and colchicine in regard to treatment of "acute intermittent" and "chronic" gout we find in Table X that 170/179 (95 per cent) in the acute category re-

TABLE X. RESPONSE TO TREATMENT IN PRIMARY AND SECONDARY GOUT

AGENT	RESPONSE	PRIMARY GOUT				SECONDARY GOUT		TOTAL	
		ACUTE INTERMITTENT		CHRONIC				NO. OF PATIENTS	PER CENT
		MALES	FEMALES	MALES	FEMALES	MALES	FEMALES		
Phenylbutazone		131	48	136	49	9	5	378	100
	Good	118	38	107	35	6	2	306	81
	Fair	7	7	14	10	1		39	10
	Poor	6	3	15	4	2	3	33	9
	Worse								
Colchicine, oral		115	35	167	45	3	2	367	100
	Good	90	17	114	25	1	1	248	68
	Fair	9	10	20	6	1		46	12
	Poor	16	8	33	14	1	1	73	20
	Worse								
Colchicine, intravenous		9	4	13	8	1		35	100
	Good	6	3	12	5	1		27	77
	Fair		1	1	1			3	9
	Poor	3			2			5	14
	Worse								
Demecolcine, intravenous		8	2	6	4			20	100
	Good	7	2	4	2			15	75
	Fair	1		2	1			4	20
	Poor				1			1	5
	Worse								
Corticotropin		10	3	16	7			36	100
	Good	9	1	10	3			23	64
	Fair	1	1	2	3			7	19
	Poor		1	3	1			5	14
	Worse			1				1	3
Cortisone and hydrocortisone, oral		6	2	17	3			28	100
	Good	3	1	8	1			13	47
	Fair	1	1	2				4	14
	Poor	2		6	1			9	32
	Worse			1	1			2	7
Hydrocortisone, local		51	41	60	40	3		195	100
	Good	46	28	46	28	2		150	77
	Fair	2	7	6	4	1		20	10
	Poor		3	8	5			16	8
	Worse	3	3		3			9	5

sponded with "good" or "fair" result to phenylbutazone while 126/150 (84 per cent) achieved a favorable response to oral colchicine. In the chronic group 166/185 (90 per cent) responded "good" or "fair" to phenylbutazone and 165/212 (78 per cent) to oral colchicine. In secondary gout 9/14 responded to phenylbutazone and 3/5 to oral colchicine.

In 35 patients who showed a poor response to phenylbutazone, 5 were subsequently treated with intravenous colchicine. Four of these patients derived a good response. Of the 35 phenylbutazone failures, 30 were given oral colchicine in adequate therapeutic dosage and 19 (63 per cent) achieved good remission.

VOL. 2 1955

Of 39 patients who had previously failed to improve on colchicine, 27 (69 per cent) did well on phenylbutazone.

Colchicine does not induce uricosuria. Its use for the reduction of tophi has been unrewarding. While its principal role is in treatment of the acute attack, Talbott[20] has recently described a decreased attack rate among those with gout who take a daily ration of colchicine. Our experience in this study is not of the sort which would permit us either to substantiate or to question this observation, since the majority of our patients had been on colchicine therapy for variable periods before coming under our observation. They came, in fact, under our observation in most instances since colchicine had been ineffective in control of chronic manifestations or because of recurrent exacerbations. On the other hand, we are fully aware that many patients are taking daily rations of colchicine and have few acute attacks just as do the majority of gouty subjects even without treatment. This question may be studied further by comparison of colchicine with other medications suitable for daily administration or by comparison with groups of unmedicated controls. Use of the individual patient as his own "control" is somewhat misleading since there is no satisfactory rule for prognosis in gout; in fact, the severity of the disorder is reflected in the frequency of acute exacerbations.

The intravenous use of colchicine or demecolcine in sufficient amount has been a more rapid and uniform method for attaining relief in the acute attack. There has been much less gastrointestinal discomfort with intravenous medication. While the number of patients treated is smaller, the number of "poor" results has been less than with oral colchicine.

TABLE XI. DURATION OF THERAPY WITH PHENYLBUTAZONE

DAYS	NO. OF PATIENTS
0–100	249
100–199	34
200–399	34
400–599	15
600–799	13
800–999	14
1,000 plus	19
Total	378

Since phenylbutazone was found to be effective in controlling the acute manifestations of gout, its use was explored in preventing the recurrence of acute exacerbations in individuals with severe chronic gouty arthritis. The attack rate was greatly reduced among those patients receiving phenylbutazone daily. Those who had experienced attacks at the rate of 4 to 6 times per year were able to avoid exacerbations in almost all instances during maintenance therapy for periods of up to four years (Table XI). The severity of exacerbation in most instances was much less during maintenance therapy with phenylbutazone than with colchicine and salicylates. The "maintenance" dosage of phenylbutazone sufficient to prevent recurrences and to relieve the symptoms

of chronic gouty arthritis was often only 100 mg. per day, an amount too small to produce a significant increase in uricosuria. In no instance did visible tophi increase in size during prolonged daily phenylbutazone medication. Decrease in tophus size was observed occasionally; but for the specific purpose of size reduction in tophi, probenecid is more effective. It has been possible, moreover, to administer probenecid and phenylbutazone concurrently with success.

Forty patients were given probenecid. With this compound, which acts by decreasing renal tubular reabsorption of both urate and water, administration in proper dosage may be expected to yield a favorable result if it can be tolerated. It is not comparable in the same sense as the medications listed in Table X since it does not alter acute manifestations of the disorder. Since the therapeutic purpose of this drug is to prolong remissions and to decrease tophaceous deposits, we do not have sufficiently long periods of observation for critical analysis of its efficiency. The usefulness of this sulfonamide is limited by its gastrointestinal irritation, production of skin rashes, antagonistic action to salicylates, potential nephrotoxicity, and the precipitation of severe attacks of acute gouty arthritis. When tolerated among our patients it has been dramatically effective in reducing the size of tophi. For more complete and extensive studies, the reader is referred to the recent article by Bartels[1] and to the review by Boger and Strickland.[3]

VOL. 2 1955

The use of corticotropin (Table X) has not been entirely satisfactory in this group of patients perhaps because its use was generally reserved for patients refractory to or intolerant of simpler nonhormonal medication. It is possible that if it had been used more extensively and if always administered intravenously by slow drip, the percentage of "good" responses would have been higher.

Although in patients with advanced gouty arthritis, the temporary oral use of cortisone, hydrocortisone, or metacortandracin was helpful in decreasing the inflammatory reaction around joints, "good" results were seen in less than half of the patients during short-term administration. When prolonged maintenance therapy was attempted, the patients almost invariably became worse.

Hydrocortisone acetate or tertiary-butyl-acetate injected locally into joints, bursae, or into inflamed tissue adjacent to tophi gave "good" or "fair" results in 87 per cent of 195 patients. The local use of this substance is of greatest value in gout, after general subsidence of an attack, to treat a single joint in or around which activity persists. In 9 instances there was increase in pain for 24 to 48 hours following local application of hydrocortisone.

CLINICAL TOXICITY

In evaluation of side-effects and sensitivity reactions to medication in gout several considerations are worthy of emphasis. Discontinuance of medication may be due to predictable side effects (e.g., fluid retention) which often are a function of dosage, sensitivity reactions (e.g., rash or urticaria), or patient refusal based upon vague symptoms of "not feeling just right."

In Table XII the frequency of discontinuance of medications due to toxicity is presented. In groups of comparable size the discontinuance of colchicine and phenylbutazone was almost identical.

TABLE XII. TOXICITY OF ANTIGOUT AGENTS

AGENT	NUMBER OF PATIENTS TREATED	PER CENT DISCONTINUED DUE TO TOXICITY
Phenylbutazone	378	5
Colchicine, oral	367	4
Colchicine, intravenous	35	14
Demecolcine, intravenous	20	5
Corticotropin	36	11
Cortisone and hydrocortisone, oral	28	11
Hydrocortisone, local	195	0.5
Probenecid	40	33

Among 367 patients treated orally with colchicine, 83 (23 per cent) suffered side effects of medication. Twenty-three (28 per cent) of these 83 had had untoward effects from a variety of previous medications. The majority of the side effects following colchicine were nausea, vomiting, and diarrhea, which are more or less a function of dosage, although a few patients present these symptoms after one or two doses. In addition to these gastrointestinal disturbances, we observed 3 instances of weakness of leg muscles following prolonged colchicine administration. The weakness slowly disappeared after discontinuance of medication. This clinical observation is in conformity with the experimental demonstration of diminished skeletal muscle strength after prolonged administration of colchicine to animals.[6] There were also several instances of urticaria and dermatitis. Medication was discontinued due to these side effects in 4 per cent of the 367 patients who received oral colchicine.

Following prolonged administration of small daily oral dosage of colchicine, a refractory state develops and the use of full therapeutic dosage is not effective. After a rest period of several weeks or following medication with corticotropin, the desired responsiveness to colchicine is often regained.

Gastrointestinal upsets are observed uncommonly following intravenous use of colchicine or demecolcine (Colcemide). Thrombophlebitis where colchicine is administered intravenously has been observed in 8 instances. This phlebitis is extremely painful and persists for at least three weeks. There is usually extension of the pain distally to the base of the thumb and proximally to the axilla on the affected side. We have not observed such venous irritation with demecolcine.

Untoward reactions to phenylbutazone occurred in 138 (32 per cent) of 378 patients. Of these 138, 35 (25 per cent) gave a history of 48 different toxic manifestations associated with previous medication of various kinds. Among the 35 patients there had, in fact, been 6 reactions to penicillin, 6 to sulfonamides, 6 to salicylates, 1 to cinchophen, 6 to opiates, 3 to procaine, 3 to gold, 2 to mercurials, 1 to iodides, and 1 to tetanus antitoxin.

Among 240 patients who showed no untoward effect from phenylbutazone, 40 (17 per cent) had a history of 49 instances of drug toxicity from other medication. In this group of 40 there were 11 instances of sulfonamide toxicity and 8 of penicillin toxicity. There was only 1 previous reaction to salicylate, 1 to cinchophen, and there were 2 reactions to iodides and 4 to opiates.

Twenty (5 per cent) of 378 patients were unable to tolerate phenylbutazone. Nine were in the acute intermittent and 11 were in the chronic gouty category. Nine were female and 11 were male. Of the 20 patients, 6 had suffered previous untoward reactions from other drugs including gold, salicylates, procaine, and penicillin. In the group of 20 who could not tolerate phenylbutazone, concurrent medications included salicylates (9 patients), sex hormones (7), barbiturates (8), antibiotics (5), thyroid (8), and multiple vitamins (12 patients). In contrast, among 304 patients who did tolerate phenylbutazone, concurrent medications included salicylates (35 per cent), sex hormones (31 per cent), barbiturates (23 per cent), antibiotics (24 per cent), thyroid (19 per cent), and multiple vitamins (40 per cent).

The toxic manifestations following phenylbutazone therapy did not vary from those previously reported in gout.[14] Ninety males experienced 121 toxic side reactions and 45 females 66 reactions. One half of the untoward reactions were gastrointestinal disturbances, among which were 3 likely and 6 possible instances of peptic ulcer activation. Fluid retention was a problem in 31 patients. There were 9 instances of transient neutropenia, one of anemia, and one of thrombocytopenia. Fifteen of the 378 patients showed rash (4 per cent). One male who had received parenteral medication elsewhere during previous weeks experienced a transient jaundice which resembled infectious hepatitis.

Probenecid produced toxicity in 20 of 40 patients and had to be discontinued in 13 (33 per cent). We realize that this is a small series and as such should probably not be compared with the larger groups treated with other agents. Exacerbation of acute gouty arthritis was observed in 3 instances. There were 10 instances of gastrointestinal distress including epigastric pain, nausea, and diarrhea. Headache, drowsiness, urinary frequency, and rash were also observed.

The toxicity of corticotropin and of the adrenal steroids used in these patients did not deviate from the well-recognized pattern of side effects of these substances. Four of 36 patients treated with corticotropin were unable to tolerate the medication and 3 of 28 treated with the steroids were forced to discontinue due to toxic side effects. There were 3 acute exacerbations of gout with steroid medication administered orally. Only 1 of 195 patients given local injections of hydrocortisone had to discontinue due to increased articular pain.

SUMMARY

A clinical analysis of 504 examples of primary and 16 of secondary gout has been made. The group included 373 males and 131 females with primary gout. Visible tophi were present in 13 per cent of males and 3.8 per cent of females. Initial serum uric acid determinations were below 6 mg. per 100 ml. in 27.5 per cent of males and in 41 per cent of females. These determinations were often made following medication with uricosuric agents. Comparison of colorimetric and enzymatic (uricase) estimations of serum uric acid revealed no practical advantage in favor of the latter.

The coincidence of other diseases is recorded. The cause of death in 18 gouty patients is reported. Alcoholism and uremia were observed much less frequently than is commonly presumed.

VOL. 2 1955

Special laboratory investigations in a few of these patients included "atherogenic indices" which were generally elevated. Serum glutamine and glutathione, were all within normal range.

For treatment of acute gouty arthritis, effective agents include colchicine, corticotropin, demecolcine, and phenylbutazone. As an adjunct measure the local injection of hydrocortisone was valuable. Less effective and often actually aggravating were oral cortisone, hydrocortisone, and metacortandracin. In the management of chronic gouty arthritis phenylbutazone and probenecid, singly or in combination, appear to be of greatest merit.

Of the currently available antigout agents phenylbutazone is the single most effective remedy, valuable at once in termination of acute gouty arthritis, prevention of acute exacerbations, and control of chronic gouty arthritis.

The undesirable side effects of the various antigout agents are discussed.

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A COMPARATIVE STUDY OF MERSOBEN, MERCUHYDRIN (PARENTERAL DIURETICS), NEOHYDRIN, AND DIAMOX (ORAL DIURETICS)

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VOL. 2 1955

PARENTERALLY administered diuretics are indicated primarily for the treatment of patients with severe heart failure. When the failure is mild to moderately severe, adequate diuresis can be obtained with drugs given orally.[1-5] Recently, interest has centered around mercurial agents which are effective orally and carbonic anhydrase inhibitors which are also given by this route. With the development of new compounds, there is a need for comparative studies in patients with congestive heart failure in order to determine what can be accomplished with the use of these newer therapeutic agents as compared to the ones in current use. The following study was conducted for the purpose of comparing the diuretic potency of two parenteral mercurial diuretics, meralluride (Mercuhydrin) and Su-1775 (Mersoben*), and two oral diuretics, a mercurial, chlormerodrin† (Neohydrin), and a nonmercurial, acetazoleamide‡ (Diamox).

METHOD OF STUDY

Two parenteral mercurial diuretics, meralluride (Mercuhydrin) and Mersoben (Su-1775), and two oral diuretics, a mercurial, Neohydrin and a nonmercurial, Diamox, were tested. Eleven ambulatory patients with moderately severe congestive heart failure were used for the study which was conducted in an outpatient cardiac clinic. The etiologic diagnosis of heart disease was either arteriosclerotic (five patients), hypertensive (one patient), or syphilitic (five patients). The patients had previously been receiving one to two mercurial injections (2 c.c. Mercuhydrin) weekly.

The patients were weighed, and following that a dose of the parenteral diuretic was administered; or in the case of the oral diuretics, the patient was given the first dose in the clinic with detailed instructions on how to continue the medication in four divided doses for two days. The weight was again recorded two days later. The patient then returned to the clinic one week after the control weight, when the weight was again recorded, a diuretic was administered, and the process repeated. Each patient was rotated through a

*3-[2 hydroxy-3(D-gluco-pentahydroxyhexyl-mercapotomercuri)-propyl] -D-mannitol, furnished by Ciba Pharmaceutical Products, Inc.

†Furnished as Neohydrin by Lakeside Laboratories, Inc.

‡Furnished as Diamox by Lederle Laboratories, Inc.

series of dose cycles for each diuretic drug. The procedure was first to administer a large dose of each of the four drugs, then a medium dose, and finally a small dose, followed again by the large dose one week later. The first diuretic to be administered to each of these patients was divided among the four agents to be evaluated. Otherwise, there was no selection of patients for any particular drug schedule. The doses studied for the parenteral diuretics were 0.5 c.c.,* 1 c.c., and 2 c.c.

The doses for oral Neohydrin were 4, 6, and 8 tablets† administered daily for 2 days; those for Diamox were 500, 1,000, and 2,000 mg. administered daily for two days. Eight patients were rotated through each dose level one time and were then given the maximum dose a second time. Three patients were not rotated through the medium and smaller doses, since the severity of failure in these three cases was such that it appeared feasible to administer only the large dose to them. The total number of test doses for each diuretic drug is shown in Table I. The number of test doses was 8 for the smallest and medium doses, and 22 for the large dose of each drug. The observations are matched using the same patients for equivalent doses of each drug. Finally, the weight differences occurring from control to two days, control to seven days, and two to seven days were subjected to statistical analysis.

RESULTS

There was little clinical evidence (other than weight gain) of progressive heart failure in any of the patients. Several patients showed a slight increase in peripheral edema, and one patient who received only 0.5 c.c. of Mercuhydrin showed marked dyspnea one week later. In a few instances, there was evidence of progressive failure on smaller doses of the drug; therefore three patients with relatively severe heart failure received only the largest doses throughout the study. These same patients had previously (prior to their inclusion in the current study) required diuretic therapy not only in larger doses but also more frequently than once a week (as in the current study) if they were to be controlled adequately. Statistical analysis of the weight response to specific doses of the parenteral and oral diuretics is summarized in Table I.

Toxicity was not remarkable throughout this study. One of the patients complained of paresthesia about the mouth, and another complained of nausea while receiving Diamox. Two patients developed diarrhea while taking Neohydrin, and one experienced nausea. However, these complaints cleared up immediately when the Neohydrin was stopped.

After parenteral administration, three patients complained of local pain after Mercuhydrin administration and two complained of pain after Mersoben. In none of these was there objective evidence of an inflammatory tissue response. One patient experienced muscle cramps after both Mercuhydrin and Mersoben administration.

Neohydrin.—Eight patients received doses of 4 and 6 tablets of Neohydrin daily for two days. Eleven patients were given 8 tablets daily for two days, the total number of test periods being twenty-two. There was no statistically

*One cubic centimeter (c.c.) contains approximately 40 mg. of mercury.
†Each tablet contains diuretic in amounts equivalent to 10 mg. of mercury.

TABLE I. STATISTICAL ANALYSIS* OF WEIGHT RESPONSE TO INCREASING DOSES OF PARENTERAL (MERCUHYDRIN, MERSOBEN) OR ORAL (NEOHYDRIN, DIAMOX) DIURETICS

DRUG SCHEDULE	NUMBER OF TREATMENT DOSES	MEAN WEIGHT CHANGE IN POUNDS ± STANDARD ERROR			P VALUE† (<)		
		C–2 DAYS‡	C–7 DAYS§	2–7 DAYS‖	C–2 DAYS†	C–7 DAYS§	2–7 DAYS‖
Neohydrin (oral)¶							
4 tablets (40 mg. Hg)	8	−0.4 ± .38	−0.5 ± .62	+0.1 ± .38	NS	NS	NS
6 tablets (60 mg. Hg)	8	−2.0 ± .69		+2.0 ± .70	0.05	NS	0.05
8 tablets (80 mg. Hg)	22	−3.0 ± .53	+0.6 ± .45	+3.6 ± .44	0.001	0.20	0.001
Diamox (oral)**							
2 tablets (500 mg.)	8	−2.2 ± .40	−0.2 ± .88	+2.0 ± .89	0.001	NS	0.10
4 tablets (1,000 mg.)	8	−2.3 ± .59	−0.9 ± .77	+1.4 ± .61	0.01	0.30	0.10
8 tablets (2,000 mg.)	22	−2.1 ± .49	−1.2 ± .61	+0.9 ± .53	0.001	0.10	0.20
Mercuhydrin (intramuscular)							
0.5 c.c. (20 mg. Hg)	8	−1.3 ± .34	+0.2 ± .55	+1.4 ± .61	0.01	NS	0.10
1 c.c. (40 mg. Hg)	8	−2.5 ± .57	−0.5 ± .85	+2.0 ± .93	0.01	NS	0.10
2 c.c. (80 mg. Hg)	22	−3.1 ± .40	−0.7 ± .57	+2.4 ± .78	0.001	0.30	0.01
Mersoben (intramuscular)							
0.5 c.c. (20 mg. Hg)	8	−2.3 ± .57	−0.9 ± .54	+1.3 ± .78	0.01	0.20	0.20
1 c.c. (40 mg. Hg)	8	−2.9 ± .83	−0.4 ± 1.07	+2.4 ± .69	0.01	NS	0.01
2 c.c. (80 mg. Hg)	22	−4.2 ± .52	−0.6 ± .47	+3.6 ± .68	0.001	0.30	0.001

*Statistical analysis by R. A. Seibert.

††$t = \bar{x}\sqrt{\frac{n(n-1)}{S x^2}}$; only P values less than 0.05 are statistically significant; NS − > P0.30.

‡Comparing control weight with weight 48 hours later.

§Comparing control weight with weight 7 days later.

‖Comparing weight 48 hours after drug administration with weight 7 days after drug administration.

¶Each tablet contained 20 mg. of diuretic which contains 10 mg. Hg.

**Each tablet contains 250 mg. of Diamox.

VOL. 2 1955

significant weight change (all weights are recorded in pounds) after the 4 tablet dose. A significant weight reduction, however, occurred two days after the control weight with the 6 and 8 tablet doses. The weight then increased again (significantly) for both doses during the five-day period after discontinuing the drug. The mean weight reduction was more marked after the 8 tablet dose than after the 6 tablet dose ($-3.0 \pm .53$ compared to $-2.0 \pm .69$). This weight reduction was also statistically more significant with the 8 tablet dose ($P < 0.001$) than it was after the 6 tablet dose ($P < 0.05$). The weight differences between control and seven days were not significant ($P > 0.05$) for any of the doses studied, indicating that weight reduction, due to the diuretic, had been lost five days after discontinuation of the drug.

Diamox.—Eight patients were given the 500 and 1,000 mg. doses of Diamox daily for two days. The same eight patients, plus the three with severe failure, received the dose of 2,000 mg. daily for two days, making a total of 22 test doses. A comparable mean weight reduction was recorded two days after the control weight for each dose level studied. This weight reduction was statistically significant for each dose. The size of the doses used, thus, did not increase the diuretic potency; however, there was suggestive evidence that the duration of diuresis was more prolonged with the larger doses. The progressive increase in weight after Diamox was discontinued indicates a recurrence of cardiac decompensation.

Mercuhydrin.—Eight patients were given 0.5 c.c. and 1 c.c. of Mercuhydrin. Eleven patients were given 2 c.c., the total number of test doses being 22. A significant weight loss occurred after each of the 3 levels of dosage from control to two days; however, it was more marked after the 2 c.c. dose. The weight increased after each dose during the two- to seven-day period, but returned to the control levels only after the 0.5 dose. However, weight reduction from control to seven days was not significant for any of the doses used, indicating that the diuretic effect had largely been lost between the second and seventh day after administration of Mercuhydrin for all doses studied.

Mersoben (Su-1775).—Eight patients received 0.5 c.c. and 1 c.c., and eleven patients, 2 c.c. of Mersoben, the total number of test doses being 8 for the 0.5 c.c. and 1 c.c. doses, and 22 for the 2 c.c. dose. A significant weight loss occurred after each dose from control to two days. The mean weight loss increased as the dose increased. The weight increased from the second- to seventh-day period, but this was significant only after the 1 and 2 c.c. doses. There was no significant weight difference after seven days, compared to the control value with any of the doses studied.

The results of the weight response to specific doses of the four diuretics studied indicate that parenteral Mersoben (Su-1775) was the most potent diuretic studied. It was not only more potent than Mercuhydrin, but was also consistently more potent than the oral diuretics in the dosage ranges employed in this study. Neohydrin was the more potent oral diuretic when an adequate dose was given. When large enough doses (6 tablets or more) were used, diuresis increased progressively as the dose of Neohydrin was increased, whereas maximum diuresis was observed with 500 mg. of Diamox and did not increase, irrespective of the size of the dose, above this level.

VOL. 2 1955

COMMENT

In so far as dosage response is concerned, comparing Neohydrin and Diamox, (Fig. 1), several deductions are suggested by the current study. Six to seven tablets (equivalent to 60 to 70 mg. Hg) of Neohydrin per day, given for two days, appears to be approximately equivalent to 500 mg. of Diamox per day, given for the same period of time. Diamox* produces its maximum diuretic effect at this dose and increasing the dose produces no additional diuresis. On the contrary, when the dose of Neohydrin is increased (above the 60 mg. Hg equivalent dose), a greater diuretic response is observed. This would suggest that, in the patient with mild heart failure, Diamox and Neohydrin are both adequate in so far as weight loss is concerned, when these drugs can be given intermittently as they were in the current study. However, in the patient with severe heart failure, when maximum diuresis is desired, Diamox is of limited value and Neohydrin becomes by far the superior oral diuretic. In addition, tolerance to Diamox develops, making it necessary to give the drug intermittently, which decreases its value in the therapy of patients with severe heart failure when a continuous diuretic response is mandatory.

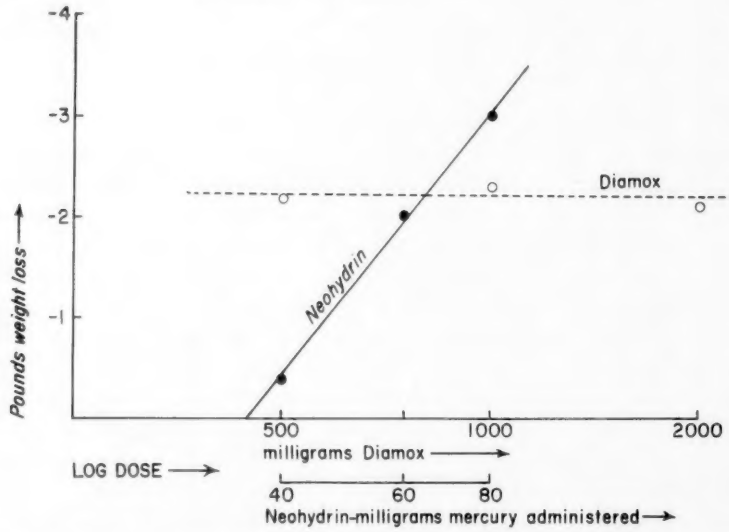

Fig. 1.—Dosage response curves comparing two oral diuretics: the mercurial, Neohydrin, with the carbonic anhydrase inhibitor, Diamox.

The dosage response curve obtained from the current studies confirms the previous observations of Greiner and his associates,[6] that Mercuhydrin produces a dosage response curve showing a geometric progression between the 0.5 and 2 c.c. (equivalent to 20 to 80 mg. Hg) doses. Increasing the dose above this level has very little additional diuretic effect.[6] The dosage response curve of Mersoben obtained from the current study indicates that the diuretic effect is still increasing progressively at the 2 c.c. dose. Mersoben and Mercuhydrin

*The dose response curve is somewhere below 500 mg. Diamox per day.

follow a similar and parallel dosage response curve, but Mersoben appears to be more potent than Mercuhydrin (Fig. 2), both in the smaller and the larger doses* employed in the current study. For example, a dose of Mersoben equivalent to 20 mg. of Hg (0.5 c.c.) appears to be approximately equivalent to a dose of Mercuhydrin containing 35 to 40 mg. Hg (0.8 to 1 c.c.), and, in this dose range, both are equivalent to from 500 to 2,000 mg. of Diamox. These observations

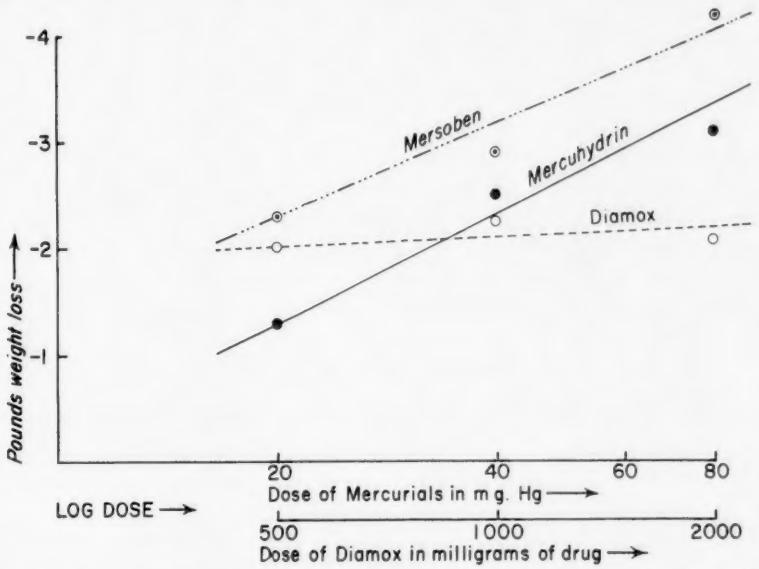

Fig. 2.—Dosage response curves comparing two parenteral mercurial diuretics (Mersoben and Mercuhydrin) with the orally administered carbonic anhydrase inhibitor, Diamox.

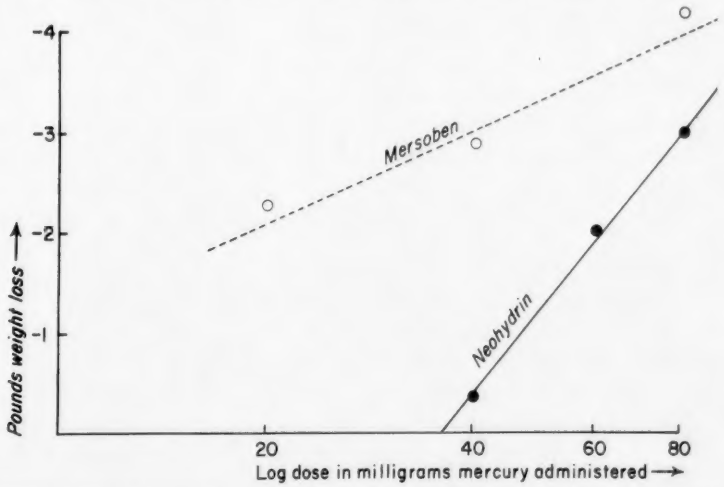

Fig. 3.—Dosage response curves comparing the parenteral mercurial, Mersoben, with Neohydrin administered orally.

*In the current study, the 80 mg. dose is statistically more valid since twenty-two observations were made as compared to eight in which the smaller doses were employed.

suggest that a significant indication for Mersoben would be in the patient with severe heart failure who requires a diuretic of greater potency than is available at maximum doses of currently available mercurial diuretics which are administered parenterally.

When Mersoben, given parenterally, is compared with Neohydrin, given orally (Fig. 3), parallel curves are not obtained but both show linear responses. Mersoben is effective at a much smaller dose equivalent of Hg than in the case of Neohydrin. This is no doubt due to the method of administration and relatively poor absorption of Neohydrin from the intestinal tract, as compared to Mersoben which was given parenterally. As a result, it is necessary to administer a relatively large amount of Neohydrin before an adequate amount is delivered to the kidneys to reach the diuretic threshold in the renal tubules. However, as the diuretic threshold to Neohydrin is exceeded, the dosage response curve rises very rapidly, so that the diuretic response to 1 c.c. Mersoben (equivalent to 40 mg. Hg) and 8 tablets of Neohydrin (equivalent to 80 mg. Hg) will approximate each other; and Neohydrin given orally will produce a degree of diuresis equivalent to that produced by Mersoben given parenterally in these doses.

VOL. 2 1955

SUMMARY AND CONCLUSIONS

1. Observations have been made on the dosage response to four diuretics, as measured by weight reduction in patients with heart failure. The diuretics studied included Mercuhydrin and Mersoben (Su-1775) administered parenterally, and Neohydrin and Diamox administered orally.

2. Five hundred milligrams per day of Diamox, given for two days, appeared to be about equivalent to 6 to 7 tablets (containing 60 to 70 mg. Hg) of Neohydrin per day, given for the same period of time. The 4-tablet dose (equivalent to 40 mg. Hg) of Neohydrin did not produce a demonstrable weight loss. When the dose of Diamox was increased above 500 mg. per day there was no increase in weight loss. However, increasing the dose of Neohydrin above 6 tablets produced an increase in diuretic response. This leads to the conclusion that Diamox is indicated primarily for the treatment of patients with mild congestive heart failure and is equally as effective as Neohydrin in these patients when intermittent diuresis of this magnitude is adequate. However, in patients with moderately severe and severe cardiac failure, Neohydrin is the oral diurectic of choice.

3. Mersoben, which contains 40 mg. Hg per cubic centimeter, is more potent than equal amounts of Mercuhydrin, which also contains 40 mg. Hg per cubic centimeter. These observations suggest that Mersoben is superior for the treatment of patients with severe congestive heart failure who do not obtain an adequate response to currently available mercurial diuretics which are administered by the parenteral route.

4. The dosage response curve of Neohydrin, administered orally, approaches the diuretic response curve of Mercuhydrin and Mersoben, when adequate doses of Neohydrin (8 tablets or more) are given daily for two days; all are more potent than doses of 500 to 2,000 mg. of Diamox given daily for an equal period of time.

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A COMPARATIVE STUDY OF NEOHYDRIN AND DIAMOX WHEN USED ALONE AND IN COMBINATION FOR THE TREATMENT OF SEVERE CONGESTIVE HEART FAILURE

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VOL. 2 1955

WHEN acute weight loss is used for comparing the diuretic potency of Diamox* and Neohydrin,† both agents appeared to be approximately equal at fixed doses of Neohydrin equivalent to 60 to 70 mg. Hg (6 to 7 tablets) and 500 mg. of Diamox. At these dosage levels, both compared favorably with Mercuhydrin (meralluride) in doses equivalent to 35 to 40 mg. Hg (0.8 to 1 c.c.), administered by the parenteral route.[1] When larger doses of these agents were used, Neohydrin was increasingly more effective than Diamox, as estimated by acute, single dose response. When 8 tablets of Neohydrin (equivalent to 80 mg. Hg) were used, the resulting diuresis compared favorably with a larger dose of Mercuhydrin (2 c.c. which contains 80 mg. Hg). However, these single dose response studies did not allow an estimation of therapeutic effectiveness of these agents when used for prolonged periods as therapy for congestive heart failure.

The diuretic potency of prolonged therapy with Diamox and Neohydrin, when used alone and in combination for the treatment of heart failure, was observed in the following study using 250 mg. of Diamox twice a day and Neohydrin in a dosage equivalent to 20 mg. Hg (2 tablets), four times a day. The purpose was to test the therapeutic effectiveness of these agents when used alone (as the only diuretic agent) and in combination, in order to test additive diuretic activity, since the mode of action is dissimilar. Diamox inhibits carbonic anhydrase in the renal tubules, specifically blocking the reabsorption of cations (sodium and potassium); whereas, Neohydrin is a mercurial diuretic which blocks reabsorption of both sodium and chloride, presumably by renal succinic dehydrogenase inhibition.

METHODS

Eighteen ambulatory patients with congestive heart failure were treated with the oral diuretics, Neohydrin and Diamox, separately and in combination, for the purpose of evaluating the comparative diuretic potency. The clinical status of the patients prior to treatment is summarized in Table I. The etiology of the heart disease was varied (arteriosclerotic, hypertensive, rheumatic, and syphilitic). By the classification of functional capacity according to the criteria

*Diamox is acetazoleamide or (2-acetylamino-1, 3, 4-thiodazole-5-sulfonamide), furnished by Lederle Laboratories.

†Neohydrin is chlormerodrin or (3-chloromercuri-2-methoxypropylurea), furnished by Lakeside Laboratories.

TABLE I. CLINICAL STATUS OF PATIENTS PRIOR TO THERAPY WITH THE ORAL DIURETICS, NEOHYDRIN AND DIAMOX, ADMINISTERED ALONE AND IN COMBINATION

PATIENT	AGE	SEX	RACE	ETIOLOGIC	ANATOMIC	PHYSIOLOGIC	FUNCTIONAL	PREVIOUS TREATMENT			
								LSD	DIGITALIS	MERCUHYDRIN	OTHER
1. D.C.	79	M	N	ASHD	Mild left ventricular enlargement	Sinus rhythm	II	1	1	2 times a week	0
2. A.S.	67	M	N	Syphilitic HD	Marked LVH; aortic insufficiency	Auricular fibrillation	III	1	1	2 times a week	NH_4Cl
3. N.P.	46	M	N	HCVD	Marked generalized cardiac enlargement; functional tricuspid insufficiency	Sinus rhythm	IV	1	1	3 times a week	Diamox
4. J.J.	67	M	N	ASHD	Marked generalized cardiac enlargement	Auricular fibrillation	III	1	1	3 times a week	0
5. W.A.	68	M	N	ASHD & HCVD	Marked LVH	Sinus rhythm	III	1	1	3 times a week	Diamox
6. M.I.	60	F	W	ASHD	Moderate LVH; aortic stenosis	Sinus rhythm	II	1	1	2 times a week	NH_4Cl
7. W.D.	51	M	N	RHD	Marked LVH; mitral insufficiency and aortic stenosis	Sinus with frequent PVC's	II	1	1	2 times a week	0
8. D.W.	58	M	W	ASHD	Moderate LVH	Sinus rhythm	III	1	1	2 times a week	NH_4Cl
9. H.M.	66	F	W	RHD	LVH, RVH, left atrial enlargement, aortic stenosis, mitral stenosis and insufficiency	Auricular fibrillation	IV	1	1	3 times a week	0
10. E.W.	76	M	N	ASHD	Moderate LVH	Sinus rhythm	III	1	1	3 times a week	0
11. J.A.	60	M	W	ASHD	Marked LVH	Auricular fibrillation	III	1	1	2 times a week	0
12. H.T.	67	M	N	ASHD	No evident cardiomegaly	Sinus rhythm	II	1	1	1 time a week	0
13. H.C.	53	F	N	Syphilitic HD	Moderate LVH; aortic insufficiency	Sinus rhythm	III	1	1	1 time a week	0
14. J.W.	55	F	N	Syphilitic HD	Moderate LVH; aortic insufficiency	Sinus rhythm	III	1	1	1 time a week	0
15. J.T.	54	M	N	Syphilitic HD	Marked LVH; aortic insufficiency	Sinus rhythm	III	1	1	1 time a week	0
16. M.W.	70	F	N	ASHD	Mild LVH	Sinus rhythm	II	1	1	1 time a week	NH_4Cl
17. O.C.	55	M	N	ASHD & HCVD	Marked generalized cardiac enlargement	Sinus rhythm	III	1	1	1-2 times a week	NH_4Cl
18. L.G.	48	M	W	RHD	General cardiac enlargement; aortic insufficiency and stenosis, mitral insufficiency and stenosis	Auricular fibrillation	II	1	1	1 time a week	NH_4Cl

Key to Abbreviations:

W—White.
F—Female.
M—Male.
N—Negro.
ASHD—Arteriosclerotic heart disease.
HCVD—Hypertensive cardiovascular disease.
RHD—Rheumatic heart disease.
Syphilitic HD—Syphilitic heart disease.
LVH—Left ventricular hypertrophy.
RVH—Right ventricular hypertrophy.
LSD—Low salt diet.
NH_4Cl—Ammonium chloride administered on three consecutive days of each week.
PVC's—Premature ventricular contractions.

of the American Heart Association, six patients were class II, ten were class III, and two were class IV. Generally, these patients had more severe disease than those included in the previous study.[1] This was possible since the patients in the current study were receiving continuous therapy, whereas, the patients in the previous study received the diuretics at weekly intervals only.

All patients were already receiving digitalis and a low salt diet. This was not altered during the study. One to three intramuscular injections of meralluride (Mercuhydrin) per week had been required for control of cardiac decompensation prior to the current study. These were discontinued. The procedure for the study was to administer the two experimental oral diuretics alone and in combination for periods of one month. The patients were divided into three groups of six patients each. During the first month, Neohydrin and Diamox were given alone to two groups of six patients each and in combination to the remaining six patients. Then, following a short control period, during which time no diuretic therapy was given, each group was given one of the three diuretic regimens which they had not previously received, for another month. During the third month, and after another brief control period, each group was changed to the diuretic, or combination of the two, which they had not received as yet. Some of the patients received additional courses of therapy with either Neohydrin or Diamox alone. Finally, to most patients the two diuretics in combination were then administered again during a fourth period.

Patients who developed increasing congestive heart failure during therapy with a single agent were usually transferred to the other diuretic, for comparison. In one instance of excessive diuresis, therapy with diuretic drugs was discontinued temporarily. The dose of Neohydrin was 8 tablets (80 mg. Hg) daily, administered in divided doses with meals and at bedtime. Diamox was given in doses of 250 mg. twice daily for five consecutive days of each week, since it was observed previously[1] that maximum diuresis was obtained with this dose, and, increasing the dose produced no additional response. Patients were examined carefully at weekly intervals during the study, and accurate weight recordings were obtained at the time of each examination. Plasma sodium and potassium determinations were done on most patients before and after a month of treatment with Neohydrin alone, Diamox alone, and both drugs in combination.

RESULTS

Results, after one month of continuous therapy with Diamox and Neohydrin administered alone and in combination, are tabulated in Table II. The rotation procedure is not indicated in the Table; but instead, the results are tabulated according to the drug or drug combination that they received.

Neohydrin Alone.—Eighteen patients received continuous therapy with 8 tablets of Neohydrin daily (80 mg. Hg) for periods of one month. Five patients received two or more courses of therapy. There was a statistically significant weight reduction for the group, both after two weeks ($p < 0.001$) and after four weeks ($p < 0.01$) of continuous therapy. The mean weight reduction was 3.1 pounds after two weeks, and 4.7 pounds after four weeks of therapy, indicating that the weight response was greater after four weeks than after two weeks.

VOL. 2 1955

The clinical status of congestive heart failure closely paralleled the weight response. Only one patient (No. 6, Table II) failed to demonstrate satisfactory clinical control of congestive heart failure. This occurred during a second course of therapy with Neohydrin. Previous diuretic therapy in this patient consisted of 2 c.c. of intramuscular Mercuhydrin twice weekly and oral ammonium chloride on three consecutive days of each week. Five patients in the group (Table I) required three injections of Mercuhydrin weekly for adequate control of congestive heart failure prior to treatment with Neohydrin. In four of the latter, cardiac status improved during the period of treatment with Neohydrin, and in the fifth, the cardiac status remained unchanged. One patient (No. 12, Table II) developed excessive diuresis manifested by weakness, anorexia, nausea, occasional vomiting, and muscle cramps. Neohydrin was discontinued after two weeks in this patient. Probably he could have been adequately controlled with less side effects if the protocol had been broken and the daily dose of Neohydrin reduced. Previous diuretic treatment had consisted of intramuscular Mercuhydrin (2 c.c.) once a week. Plasma potassium concentration decreased slightly in this patient, whereas, sodium concentration was not altered significantly.

Diamox Alone.—The same eighteen patients received one or more one-month courses of therapy with Diamox. The dose was 250 mg. twice daily for five consecutive days of each week. Statistical analysis of the weight response for the group indicated that there was no significant weight reduction after two weeks ($p>0.50$) or after four weeks ($p>0.50$) of Diamox administration. The mean weight difference for the group was +0.6 pounds after two weeks, and −0.4 pounds after four weeks. As with Neohydrin, the clinical status of congestive heart failure paralleled the weight response. In six patients (33 per cent), congestive heart failure progressively increased during therapy with Diamox. As a result, the drug was discontinued after two weeks in four patients. Previous diuretic requirements in the later four patients consisted of intramuscular Mercuhydrin (2 c.c.) three times weekly in three patients, and twice weekly in one patient. One patient who developed more marked decompensation during one course of therapy with Diamox was satisfactorily controlled during another course. All four patients who developed increasing cardiac decompensation with Diamox became well controlled when transferred to Neohydrin alone or combined with Diamox. In general, these results reflect the severity of heart failure, since patients who previously required only one injection of Mercuhydrin weekly were satisfactorily controlled with Diamox alone. There was no significant alteration in the plasma concentration of potassium after one month of treatment with Diamox, whereas, sodium increased slightly (mean for the group). There was no evidence of sodium depletion.

Combined Therapy With Neohydrin and Diamox.—Eighteen patients received Neohydrin and Diamox in combination during the initial month of treatment with both drugs. Twelve of the eighteen patients were also treated for a second month with both drugs in combination, following the courses of therapy with each diuretic alone. Six patients who had obtained adequate diuresis while receiving Neohydrin alone were not given the second course of combined therapy. The results, from the standpoint of weight response, reveal that a statistically

TABLE II. CLINICAL RESULTS AND OBSERVATIONS ON PLASMA ELECTROLYTES DURING THERAPY WITH THE ORAL DIURETICS, NEOHYDRIN AND DIAMOX

PATIENT	NEOHYDRIN			DIAMOX			BOTH +			BOTH +			CLINICAL RESPONSE*				PLASMA SODIUM				PLASMA POTASSIUM			
							PERIOD 1			PERIOD 2					PERIOD 1	PERIOD 2	MEq./LITER				MEq./LITER			
	C	2 WK.	4 WK.	C	2 WK.	4 WK.	C	2 WK.	4 WK.	C	2 WK.	4 WK.	NEO.	DIA.	BOTH +	BOTH +	CONTROL	BOTH +	NEO.	DIA.	CONTROL	BOTH +	NEO.	DIA.
1. D.C.	185.5	181.0	180.0	183.0	175.5	185.5	186.0	182.5	183.0	182.5	177.0	173.5	+2	−1	+2	+3	144	148	150	136	4.3	4.0	4.9	4.8
2. A.S.	169.0	164.0	161.5	161.5	161.5	160.0	166.0	162.5	158.0	—	—	—	+2	+2	+2	—	140	140	143	151	4.8	4.7	4.7	5.7
	160.0	156.5	153.0	153.0	159.0†	—	—	—	—	—	—	—	+3	−2	—	—	—	—	—	—	—	—	—	—
	159.0	155.0	—	—	—	—	—	—	—	—	—	—	−	−	−	−	—	—	—	—	—	—	—	—
3. N.P.	169.0	165.0	164.0	159.0	169.0†	—	161.0	158.0	154.0	164.0	159.0	155.0	+2	−2	+2	+3	136	145	139	141	4.2	5.3	4.1	5.4
4. J.J.	160.5	161.0	160.5	160.0	166.0†	—	164.0	163.0	163.0	160.5	161.0	158.0	+2	−2	+2	+2	140	133	134	141	4.9	2.3	3.7	4.7
5. W.A.	154.0	136.0	126.0	126.0	123.5	133.0	148.0	145.0	144.0	123.5	124.5	122.5	+3	−1	+2	+2	138	138	137	154	3.6	3.6	4.2	3.4
	133.0	124.0	123.5	—	—	—	—	—	—	—	—	—	+2	−	−	−	—	—	138	—	—	—	2.9	—
6. M.I.	181.0	182.0	182.0	182.0	183.0	177.0	189.0	186.5	181.0	183.0	175.0	178.0	+1	+2	+2	+2	140	144	150	150	4.5	4.1	4.1	5.3
	177.0	183.0†	—	—	—	—	—	—	—	—	—	—	−2	−	−	−	—	—	—	—	—	—	—	—
7. W.D.	138.0	136.0	138.0	139.5	140.5	138.0	150.0	142.5	139.5	139.0	136.5	128.0	+2	+2	+2	+3	144	141	138	152	5.2	3.6	3.7	4.6
8. D.W.	122.5	122.0	119.0	123.5	121.5	122.5	123.0	124.0	123.5	119.0	121.0	118.0	+2	+2	+2	+2	136	140	146	139	5.1	5.1	5.7	5.0
9. H.M.	88.5	83.0	83.0	88.0	88.5	88.5	88.5	86.0	85.0	91.0	80.5	78.5	+3	+1	+2	+3	136	146	150	140	5.3	4.6	6.7	5.3
	90.0	90.0	88.5	88.5	91.0†	—	—	—	—	—	—	—	+1	−2	+2	—	—	—	—	—	—	—	—	—
10. E.W.	203.0	204.0	206.0	206.0	208.0	205.0	204.0	204.0	204.5	207.0	203.0	202.0	+1	+1	+1	+2	141	144	147	154	4.1	5.0	5.3	4.6
11. J.A.	187.0	186.0	184.0	179.0	177.0	180.0	184.0	181.5	179.0	—	—	—	+2	+2	+2	—	147	—	150	—	4.1	—	4.1	—
12. H.T.	125.0	118.0‡	—	121.0	118.0	112.5	133.0	125.5	125.0	—	—	—	+3	+3	+3	—	140	—	141	147	5.4	—	4.4	3.3
13. H.C.	148.0	146.0	149.0	149.0	148.0	148.0	148.0	145.0	146.5	148.0	146.5	147.5	+2	+2	+2	+2	144	144	148	149	4.1	4.3	4.8	4.2
14. J.W.	103.0	102.0	98.0	104.0	103.5	102.5	110.0	104.5	101.0	—	—	—	+3	+2	+3	—	137	—	150	150	4.4	—	4.1	4.2
	—	—	—	98.0	100.0	101.0	—	—	—	—	—	—	—	+1	—	—	—	—	—	—	—	—	—	—
15. J.T.	172.5	173.0	173.0	173.0	173.5	172.5	173.0	172.5	173.0	175.0	171.0	170.0	+2	+2	+2	+2	137	141	135	136	5.2	4.4	3.8	4.8
16. M.W.	104.0	98.0	99.0	105.0	102.0	104.0	111.0	108.5	100.5	—	—	—	+2	+1	+3	—	140	144	142	137	4.2	5.1	4.3	4.4
17. O.C.	146.0	143.5	141.5	141.5	142.0	142.0	144.5	142.0	146.0	148.0	139.0	140.0	+2	+2	+2	+2	145	139	140	149	3.8	4.3	5.1	4.5
18. L.G.	129.5	124.0	123.0	123.0	125.0	125.5	133.5	125.5	124.0	—	—	—	+2	+2	+3	—	136	—	148	145	5.3	—	4.0	5.3
	135.0	131.5	127.5	134.0	135.0	132.5	—	—	—	—	—	—	+2	+2	—	—	—	—	—	—	—	—	—	—

VOL. 2 1955

TABLE II—CONT'D

Mean (Weight Difference):								
C-2 and C-4 Weeks	−3.1	−4.7	+0.6	−0.4	−3.2	−4.8	−3.9	−5.8
2-4 Weeks		−1.4		+0.2		−1.4		−1.9
P Value: §<								
C-2 C-4 Weeks	0.001	0.01	0.50	>0.5	0.001	0.001	0.01	0.001
2-4 Weeks		0.05		>0.5		0.10		0.05

Key to Abbreviations:

\+ = Period of treatment with combined Neohydrin and Diamox. Period 1 is first month during which both Neohydrin and Diamox was administered. Period 2 is fourth month study period, during which time both Neohydrin and Diamox were administered.

C = Control weight at the beginning of each month of therapy.

2 Wk. = Weight after 2 weeks of therapy; C-2, mean weight change after first 2 weeks of drug administration.

4 Wk. = Weight after 4 weeks of therapy; C-4, mean weight change after 4 weeks of drug administration.

2-4 Wk. = Weight difference between 2 and 4 weeks of drug administration.

*The clinical control of congestive heart failure based on symptomotology was graded as follows: −3 to −1, inadequate control of heart failure symptoms; 0, no clinical response to drug; +1 to +3, fair to excellent control of heart failure symptoms.

†Therapy discontinued after 2 weeks because of inadequate clinical control of congestive heart failure.

‡Therapy discontinued after 2 weeks because of excessive diuresis.

§ $t = \bar{X}\sqrt{\frac{n(n-1)}{Sx^2}}$; P values > 0.05 are not statistically significant.

significant reduction in weight occurred at the end of two and four weeks of each course of combined drug administration. The weight response, however, was greater during the first two weeks of each course. The degree of weight loss for the group was remarkably similar to that which occurred with Neohydrin alone. Clinically, the status of congestive heart failure improved in all of the patients who received both drugs concurrently. Two patients manifested excessive diuresis during the second course of combined therapy. This appeared to occur more frequently in patients with less severe heart failure. When Diamox and Neohydrin were used in combination, they were slightly more effective in controlling clinical symptoms of congestive heart failure than when either drug was used alone. Plasma sodium and potassium did not change significantly after a one-month course of therapy with these agents.

VOL. 2 1955

SIDE EFFECTS

The side effects which were observed during therapy were attributable either to diuresis or to gastrointestinal irritation. Discontinuation of a scheduled course of therapy became necessary only as a result of excessive diuresis. The incidence of side effects during the use of each diuretic alone and in combination is shown in Table III. Side effects were practically nonexistent during treatment with Diamox alone. When Neohydrin was used alone or in combination with Diamox, the incidence of side effects was similar. Approximately one-fourth of the patients developed mild diarrhea, abdominal cramps, and nausea; however, vomiting rarely occurred. Anorexia and excessive weakness were manifestations of excessive diuresis and were observed in a few patients. If smaller doses of Neohydrin had been used, the incidence of side effects attributable to this drug would no doubt have been reduced.

TABLE III. SIDE REACTIONS DURING THERAPY WITH ORAL DIURETICS (NEOHYDRIN, DIAMOX) WHEN ADMINISTERED ALONE AND IN COMBINATION

	BOTH		NEOHYDRIN		DIAMOX	
	NO.	%	NO.	%	NO.	%
Total number patients treated	16	100	18	100	18	100
Side reactions:						
Diarrhea	6	33	4	22	0	0
Abdominal cramps	4	22	5	28	0	0
Nausea	6	33	5	28	1	6
Vomiting	2	11	0	0	0	0
Weakness	7	39	4	22	3	17
Anorexia	6	33	4	22	2	11

DISCUSSION

This study represents a comparative study of the diuretic potency, clinical effectiveness, and side effects of diuretic drugs. Two oral diuretics, Neohydrin and Diamox, were used alone and in combination. The method of study was

one of actual clinical trial, with the purpose of a controlled approach. The same group of patients who represented different intensities of congestive heart failure were utilized to evaluate the comparative effects during a fixed period of treatment of one month with a relatively fixed daily dose of diuretic. The method used in this study can perhaps be considered as an extension of the single dose response method for evaluating diuretic potency. This was originally described by Greiner and his co-workers,[2] and was utilized in our previous study[1] with the exception of a few minor alterations.* By this means, also, the clinical effectiveness of diuretics can be subjected to comparative evaluation.

The results indicate that Neohydrin is a more potent diuretic than Diamox. This can probably be attributed to the mode of action. Diamox depresses tubular reabsorption of sodium by depressing carbonic anhydrase activity in the kidney. The ability to increase sodium excretion by this method appears to have definite limitations. Neohydrin, being an organic mercurial, produces diuresis by its ability to depress both sodium and chloride reabsorption in the renal tubules by depression of enzymatic activity of a less specific variety. The different mechanisms of action give ample reason for comparing the diuretic effectiveness of these agents when used both alone and in combination. Patients who previously required only one injection (2 c.c.) of Mercuhydrin (meralluride) per week were generally adequately controlled by Diamox alone, but those requiring more frequent parenteral mercurial administration were not. On the other hand, patients who previously required two or three injections of Mercuhydrin per week were usually well controlled with Neohydrin alone, attesting to the greater potency of this agent.

These differences in therapeutic effectiveness are not so apparent when a single dose response curve is used for evaluating these agents. Under these circumstances, Diamox appears to be nearly as effective as 6 to 8 tablets (equivalent to 60 to 80 mg. Hg) of Neohydrin. However, when continuous diuresis is mandatory to control heart failure, Neohydrin becomes the superior agent, since this compound continues to produce diuresis when administered daily. On the contrary, Diamox is effective only when the heart failure is so mild that interrupted administration is feasible, such as giving the drug two days out of each week, as was previously done[1] when we determined a dosage response to these agents. When more frequent diuretic effect or continuous diuresis is mandatory, Diamox is inadequate, due to the apparent development of tolerance when this drug is administered too frequently.

The incidence of side effects during therapy with Diamox was low. Approximately one-fourth to one-third of the patients developed symptoms of gastrointestinal irritation during treatment with 8 tablets (80 mg. Hg) of Neohydrin daily. These symptoms were not of sufficient severity to cause discontinuation of the drug. Gastrointestinal irritation was minimized by administering Neohydrin in divided doses with meals. About one-third of the patients developed weakness and fatigue, associated with diuresis, during therapy

*Post-drug observations on weight response to the parenteral drugs were made 48 hours after administration as well as 48 hours after the oral drugs were started. The latter were given in 4 equally divided doses each day for two successive days.

with Neohydrin alone and in combination with Diamox. This was particularly prone to occur in patients with less severe congestive heart failure, who probably could have been adequately treated with smaller doses of the drug.

The use of Neohydrin and Diamox, in combination, provided a potent diuretic effect. The mean weight response during therapy with this combination was similar to that obtained with Neohydrin alone. However, the combination was more effective than Neohydrin alone in patients with severe congestive heart failure. It would appear that there are few patients with congestive heart failure who cannot be controlled satisfactorily with these oral diuretics, if they are used appropriately, alone or in combination.

SUMMARY AND CONCLUSIONS

1. Comparative observations have been made on the diuretic potency of Neohydrin and Diamox, when used alone and in combination, for the treatment of eighteen patients with heart failure. A dose of 250 mg. of Diamox given twice a day was compared with 36.6 mg. (2 tablets) of Neohydrin (equivalent to 20 mg. Hg) given four times a day.

2. The results indicate that Neohydrin is a more potent diuretic than Diamox when given for prolonged periods of time. The average weight loss for the group over a four-week period of Neohydrin administration was 4.7 pounds ($p < 0.01$), whereas, the patients receiving Diamox did not lose weight as a group, nor was there an increase in weight to indicate progressive failure.

3. Patients with mild heart failure can be adequately controlled with either Diamox or Neohydrin, whereas, patients with severe heart failure cannot be adequately controlled with Diamox alone, but require Neohydrin alone or in combination with Diamox.

4. Most patients with congestive heart failure can be treated effectively with Neohydrin or Diamox, if they are used appropriately, alone or in combination.

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VOL. 2 1955

Review

METABOLISM AND AGE

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IT IS commonly assumed that with increasing age there is a gradual slowing down of metabolic processes in the body. This belief stems from casual observations of older people who appear to move more slowly and deliberately and often are unable to maintain the same rate of performance found in their juniors. More detailed laboratory studies have shown the quantitative nature of these decrements in rate of response. These studies indicate a loss in speed of response with age in a wide variety of performances ranging from complex mental tasks[1-5] through reaction time measurements,[6,7] motor skills,[8,9] and even to physiologic processes such as the rate of recovery following experimental displacements of certain components of blood.[10,11] The common denominator of all these observations is regarded as a slowing of the metabolism of the cells of the body with advancing age. It is the purpose of this review to examine critically this concept.

Although the term "metabolism" has a variety of meanings, the present discussion will be concerned primarily with the rate of oxygen uptake determined under standard conditions, since this is our best measure of total metabolism of the organism. It is a measurement that can be determined under standard conditions for the entire animal as well as for individual tissues. Admittedly, the oxygen uptake is a gross measure which can tell us nothing about specific pathways of intermediary metabolism, but it is perhaps our most useful measurement of metabolism at the present time.

Basal Oxygen Consumption or Heat Production.—It is obvious that the total oxygen uptake of the individual depends on his size.[12] Early investigators in the field of respiratory metabolism assumed that the heat production would be determined by the heat loss and, therefore, adjusted all values to a standard unit of surface area.[13] Although we now know that the original assumption was incorrect, the use of surface area as the best estimate of body size has become traditional, even though surface area cannot be measured directly but must be calculated from height and weight.†

The data of Boothby, Berkson, and Dunn[15] offer an over-all view of age changes in basal metabolism. As shown in Fig. 1, there is a gradual decrement in basal heat production per square meter of surface area after the age of 20

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†The formula for calculating surface area is S.A. (in sq.M.) = 71.84 $H^{0.725}W^{0.425}$) where H = ht. in meters and W = wt. in Kg.[14]

years. Wide individual differences are apparent at all age levels. The general downward trend is also apparent in the data reported more recently by Robertson and Reid[16] on British subjects (Table I). The number of subjects over the age of 65 in each of these studies is very limited. For data at the higher age ranges we must turn to other sources.

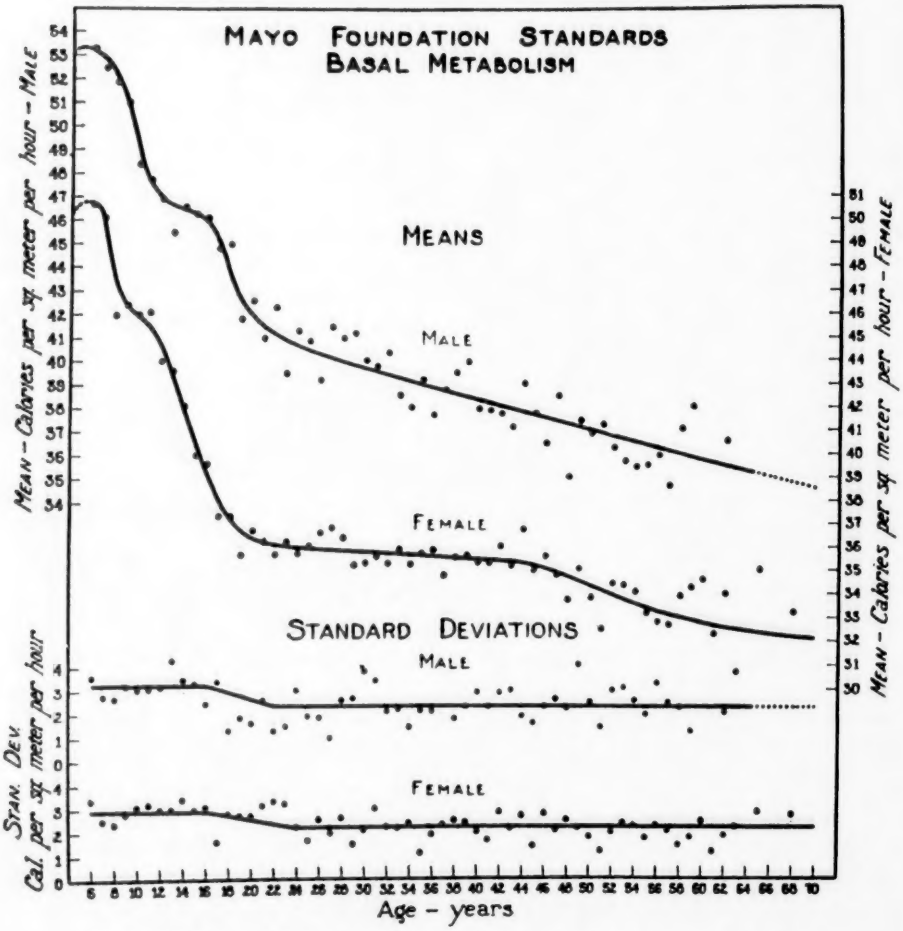

Fig. 1.—Age changes in basal metabolism. (From Boothby, Berkson, and Dunn.[15])

Fig. 2 summarizes the results from a number of studies on males and brings to light some important differences. In the first place, it shows that the level of metabolism, reported in the early studies of DuBois[17] and Boothby, Berkson, and Dunn,[15] was higher at all ages than values reported in later studies.[18] Although many of the subjects included in these series were "normal" individuals living in the community, who were tested specifically for the study, patients were also included where careful analysis of their medical histories and physical findings "gave every reason to assume that they had no disturbance of meta-

VOL. 2 1955

bolism."[15] There is very close agreement between observations made on two institutionalized populations, one from Baltimore[19] and one from St. Louis.*[20] In contrast, the results obtained by Lewis[21] on a group of individuals who were still living in the community in New York showed much less decrement with increasing age than did the two institutional groups.† This difference raises an interesting question: "Is it due to sampling, or are individuals, who are participating in active community life, metabolically different from those who live a more sheltered and less active life in an institution?" Unfortunately, we cannot answer this important question at present.

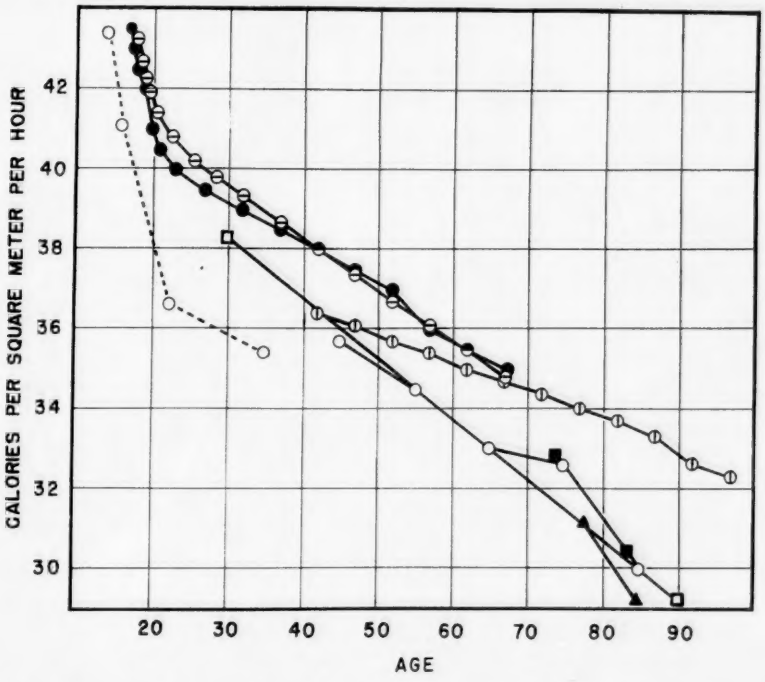

Fig. 2.—Age changes in basal metabolism of males: averages O - - - - - - - O (data from University of California adolescent study, Shock[15]); ●———● (data from Boothby, Berkson, and Dunn[15]); Θ———Θ (data from DuBois[17]); Φ———Φ (data from Lewis[21]); □———□ (data from Kountz, Chieffi, and Kirk[21]); O———O (data from Shock and Yiengst[19]); ■———■ (data from Binet and Bourlière[23]); ▲———▲ (data from Matson and Hitchcock[21]). (Curve from Shock.[52])

Scattered through the literature, a number of studies on small groups of aged subjects may be found. One of these studies was reported by Benedict[22] on 6 men and 10 women (aged 69 to 87 years) who were tested in their own homes in the morning before rising. Each subject was tested a number of times and the lowest value used. The average values for these ambulatory subjects were 31.2 for men and 30.0 cal./M²/hr. for women. The value for men is appreciably lower than the 35.1 cal./M²/hr. reported by Aub and DuBois[23] in 6

*Dr. Kirk kindly placed the original observations, made in this study, at our disposal.

†It cannot be argued that the subjects tested by Lewis were "less basal" than the institutionalized subjects, since all spent the night prior to testing in the hospital and all determinations were made in the morning before rising.

men aged 77 to 83 years. Matson and Hitchcock[24] determined the basal metabolism in 8 women (aged 77 to 106) and 14 men (aged 74 to 92) who were residents of an old people's home. The oldest subject, a bedridden woman of 108 years, 147 cm. tall and weighing 31.8 kg., had a basal heat production of only 21.07 cal./M²/hr. The average value for 6 women was 27.43 cal./M²/hr., and for 14 men was 30.11 cal./M²/hr. Values ranged from 21.2 to 29.9 cal./M²/hr. for women and 24.5 to 33.1 cal./M²/hr. for men (Table I).

TABLE I. BASAL METABOLISM AND AGE—MALES
(Cal./sq.M./hr.)

SOURCE OF DATA	AGE (YEARS)											
	40–49		50–59		60–69		70–79		80–89		90+	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
Boothby, Berkson, and Dunn[15]	103	37.65	67	36.34	13	36.52	—	—	—	—	–	—
*Robertson and Reid[16]	52	35.20	17	34.30	17	32.30	7	32.70	—	—	–	—
DuBois[17]	—	38.50	—	37.50	—	36.50	—	35.50	—	—	–	—
*Shock and Yiengst[19]	27	35.73	27	34.50	39	33.00	38	32.60	21	30.05	–	—
*Kountz et al.[20]	6	36.18	19	34.41	19	34.14	16	31.26	8	30.31	–	—
Lewis[21]	20	36.40	20	34.50	20	35.10	20	34.40	20	33.60	3	29.8
Benedict[22]	—	—	—	—	—	—	3	31.00	3	31.30	–	—
Aub and DuBois[23]	—	—	—	—	—	—	6	35.10	—	—	–	—
*Matson and Hitchcock[24]	—	—	—	—	—	—	6	31.20	8	29.30	–	—
*Binet et al.[28]	—	—	—	—	—	—	6	31.08	9	29.44	–	—
*Binet and Bourlière[29]	—	—	—	—	—	—	17	32.80	13	30.47	–	—
*Binet and Bourlière[30]	—	—	—	—	—	—	12	34.90	11	30.80	–	—
*Aaltonen[25]	—	—	—	—	—	—	—	—	6	32.70	–	—
Kisé and Ochi[26]	—	—	13	36.05	15	34.91	10	33.16	6	32.06	–	—
Weighted Mean of Studies Marked*	85	35.44	63	34.42	75	33.13	102	32.53	76	30.35	–	—

TABLE II. BASAL METABOLISM—FEMALES
(Cal./sq.M./hr.)

SOURCE OF DATA	AGE (YEARS)											
	40–49		50–59		60–69		70–79		80–89		90+	
	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN	N	MEAN
Boothby, Berkson, and Dunn[15]	113	35.36	105	33.75	33	33.63	—	—	—	—	–	—
Robertson and Reid[16]	94	32.00	31	31.50	27	31.00	8	30.50	—	—	–	—
DuBois[17]	—	36.50	—	35.00	—	34.00	—	33.00	—	—	–	—
Kountz et al.[20]	5	33.76	10	33.52	15	31.50	15	30.68	—	—	–	—
Benedict[22]	—	—	—	—	—	—	7	30.50	3	29.30	–	—
Matson and Hitchcock[24]	—	—	—	—	—	—	1	26.30	4	27.85	2	24.06
Binet et al.[28]	—	—	—	—	—	—	17	32.80	9	33.40	–	—
Binet and Bourlière[29]	—	—	—	—	—	—	34	33.70	22	32.20	–	—
Binet and Bourlière[30]	—	—	—	—	—	—	47	34.40	62	32.90	5	32.50
Aaltonen[25]	—	—	—	—	—	—	—	—	21	37.60	–	—
Kisé and Ochi[26]	—	—	8	34.02	16	33.15	18	31.90	8	30.42	–	—

VOL. 2 1955

Additional mean values, recalculated from data in the literature, are summarized in Table I. Ideally, each of the mean values shown in the table should be accompanied by a measure of variation. While it was possible to determine the standard deviation of the distribution in some of the more extensive series, in others it was not, either because the individual observations were not published or because the number of cases was too small. Hence, only average values, with the number of cases, are given. In studies in which the standard deviation of the decade distribution can be calculated, it varies between 2.5 and 4.5 cal./M²/hr. A span of ±15 per cent of the mean value will, in general, include 65 to 70 per cent of the observation. In the case of males, the values obtained, at the upper age limits (80 to 90 years), are in the neighborhood of 30 cals./M²/hr. The exceptions are the data on noninstitutionalized subjects reported by Lewis,[21] a group of German 80- to 90-year-olds reported by Aaltonen,[25] and the Japanese subjects studied by Kisé and Ochi.[26] Mention should also be made of the average value of 20.9 cal./M²/hr. reported on 12 Ukranian subjects, aged 95 to 142 years.[27] In this series, ages were estimated within a 5-year span and no information about the general health or activity of the subjects is given.

A composite value based on the more recent studies of men (aged 40 to 90) in institutional populations, including the data of Binet and his collaborators,[28-30] is given in the last line of Table I. Although there is a general decrement with age, it is relatively small (1.10 cal./M²/hr./decade) as compared with the wide range of individual differences (σ_d = 2.5-4.5 cal./M²/hr.).

Although there are a good many more elderly women than men in the population, the data on basal metabolism on women are even more scanty than those on men. With the exception of the series of observations by Boothby, Berkson, and Dunn,[15] and Robertson and Reid,[16] we are limited to a few isolated studies. Although there is a downward trend in the data, it is interesting to note that the sex difference in basal metabolic rate may become progressively less. In fact, the studies by Binet and Bourlière[30] and Aaltonen[25] report higher values in women than in men over the age of 70. Since the 80-year-old subjects studied by Benedict,[22] by Matson and Hitchcock,[24] and by Kisé and Ochi[26] showed the usual sex difference, we must have more extensive data before we can decide this question.

Quenouille, Boyne, Fisher, and Leitch[31] have analyzed statistically basal metabolism data on over 8,600 subjects collected from the literature. Of the group, 800 were aged 40 and over, and 135 were over the age of 70. On the basis of derived linear regression equations, covering the age span 20 to 90, the authors conclude that basal metabolism declines at a rate of 3 per cent per decade. This is slightly higher than the 2 per cent per decade suggested by Aub and DuBois[23] and is less than the 4 per cent per decade deduced by Kleiber[12] from a reanalysis of the data of Harris and Benedict.[32] It is in close agreement with the rate of decline calculated on the summarized data for males, shown in Table I (1.08 cal./M²/hr. as compared with 1.1 cal./M²/hr.). These authors also reported that the basal metabolism of women was almost exactly seven-eighths of that of men of the same height and weight. Their analysis did not consider the effect of age on the sex difference.

In summary, it is clear that the average values for basal metabolism per unit of surface area fall significantly with age in both men and women. The decrement is small in relation to individual differences, but is statistically significant between the ages of 30 and 90.

Individual Age Changes in Basal Metabolism.—The establishment of a significant age change in average values does not offer any information about age changes in the individual as he progresses through life. Unfortunately, longitudinal studies with systematic observations on the same individual throughout his life span have not been carried out. The few observations available from repeated tests on the same subject have been summarized in Table III, taken in part from a report by Magnus-Levy.[33] All of these subjects had extensive experience with metabolism tests so that the data are highly reliable. In four of the six subjects, the drop in basal metabolism per decade was very close to the 1.1 cal./M^2/hr./decade predicted from the average curves, but in two of the subjects rather marked deviations occurred.

VOL. 2 1955

TABLE III. AGE CHANGES IN BASAL METABOLISM IN INDIVIDUALS
(Data from Magnus-Levy: J.A.M.A. 118:1369, 1942)

SUBJECT	AGE	CAL./SQ.M./HR.	DECREMENT CAL./SQ.M./HR./DECADE
Zuntz	41	33.6	
	70	30.2	1.1
Magnus-Levy	26	38.1	
	76	31.5	1.3
Lusk	44	42.8	
	58	32.7	7.2
Benedict	38	38.2	
	57	32.7	2.8
DuBois	30	38.1	
	58	34.2	1.2
	68	34.7*	0.9
	72	33.1*	1.2
Shock	25	34.4	
	35	33.0	
	45	32.0	1.2

*Data kindly supplied by Dr. H. C. Wick.

Basal Metabolism and Degree of Senility.—Almost every investigator who has studied basal metabolism in aged subjects has attempted to relate the level of BMR to the clinical state of the individual. While it is true that Matson and Hitchcock[24] found a very low basal metabolism (21.0 cal./M^2/hr.) in a 106-year-old woman who was bedridden, most authors have stated explicitly that no relation between degree of physical impairment and basal metabolism was evident. One exception is the report of Kountz and Chieffi[34] who studied 500 patients between the ages of 40 and 90. All their metabolism data, obtained

under clinical conditions with a closed circuit technique, are reported only as the per cent of cases falling between specified limits of BMR (in age decades, as per cent deviation from "normal standards"). No age or sex breakdown of their data is given, but all 500 subjects were classified clinically either as "normal" (N = 39), early degenerative changes (N = 134), moderate degeneration (N = 132), or advanced degeneration (N = 196). The classification was apparently based on a general clinical appraisal. The advanced degeneration group was in a "state of permanent invalidism" but it is not clear as to whether or not they were bedridden. Based on an examination of the alterations in proportion of subjects showing BMR's lower than normal, the authors claim that the patients with moderate degeneration showed the greatest lowering of metabolism (93 per cent had BMR's below ±0 per cent), whereas 66 per cent of the patients classified as showing marked degeneration had BMR's corresponding to normal (±10 per cent) and 24 per cent were greater than +10 per cent (as compared with 1.4 per cent of the early degeneration group). The authors postulate a cycle whereby the early degenerative changes are accompanied by a reduction in metabolism, whereas in later stages there is an increase in metabolism which they attribute to a loss in reserves. This seems highly improbable. Furthermore, their results could well occur if the "normal" values used for BMR in the later ages were inadequate. Unfortunately, their data are not presented in a fashion that makes it possible to calculate the means and standard deviations of basal metabolism according to age or in terms of their clinical groupings.

Factors Involved in the Reduction of Basal Metabolism With Age.—The observed reduction, with age, in basal oxygen uptake (or heat production) per individual (or per unit of surface area) may be due to any of the following: (a) a reduction in the total number of functioning cells in the individual; (b) reduced responsiveness of the cells to the hormones of the thyroid gland; (c) inadequacy of the thyroid gland to produce or liberate its active principles; (d) reduced activity of the pituitary gland in stimulating the thyroid gland; as well as to alterations in metabolic activity of the functioning protoplasm.

Basal Metabolism Per Unit of Body Water.—Each of the other possibilities must be examined before we can assume a reduction in metabolic activity of individual cells or active protoplasm with age. The limitations in using either surface area or total body weight as an index of the number of functioning cells, or the active protoplasmic mass of the individual are obvious. Cells which are no longer metabolizing will continue to contribute to total weight as will any accumulation of fat or water. Histologic evidence indicates clearly that the number of functioning cells in many tissues diminishes progressively with age.[35-38] In some organs, this is accompanied by a reduction in weight, but this is not always true.[39] Clearly, we need some index that will reflect these structural changes in the tissue. Although the total water content of the intact human being diminishes with age,[40,41] the intracellular water of tissues remains constant throughout life. This has been demonstrated in the rat by studies of Lowry and Hastings,[42] using histochemical techniques. Thus, the water content of

the intact animal may be a closer index of the amount of functioning protoplasm than either surface area or weight.*

With the availability of methods for estimating the total body water of the intact human being,[51] it is possible to utilize this measurement as an index of the amount of protoplasm in the subject. Comparisons of total body water and basal metabolism have been made in 94 subjects between the ages of 19 and 95 years.[40,52] The subjects were all ambulatory males selected from the wards of the Baltimore City Hospitals and the Old People's Home. Subjects with pathologic states that might influence fluid volume or basal metabolism, such as

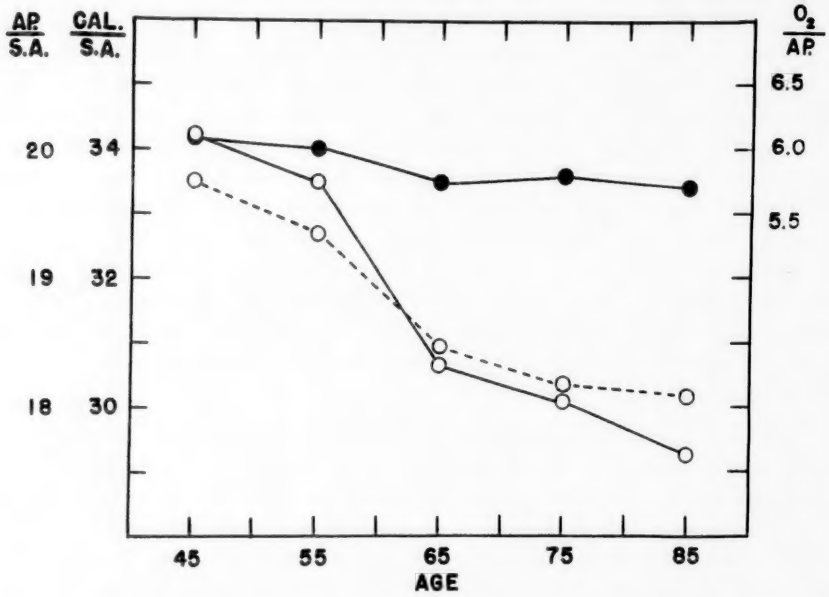

Fig. 3.— O - - - - - - - O total body water; liters per sq.m. O——— O basal metabolism, cal./sq.M./hr. ●——— ● basal oxygen uptake, c.c./min./l. total body water. (From Shock.[52])

edema or thyroid disease, were excluded on the basis of clinical and laboratory examinations. All subjects were maintained on a special ward under standardized conditions during the test period and no patient was studied unless he had been in the hospital or home for at least one month.

Simultaneous determinations of plasma volume, thiocyanate space, and total body water were made by the infusion of 50 ml. of an isotonic solution

*The concept of "lean body mass" as the appropriate index for physiologic measurements has been proposed and utilized by a number of investigators.[41,43-48] Lean body mass may be computed by formula from body water estimates using a factor determined empirically from animal studies,[49] or from measurements of specific gravity. The logic of this approach is somewhat different; i.e., correction for the accumulation of fat, but the end result is the same.

Dahlstrom[50] has proposed the use of extracellular fluid (thiocyanate) space as a measure of "metabolic size." In a series of 23 adults (all but 4 were below the age of 40) a high correlation (r = .96) between predicted heat production and thiocyanate space was obtained. Since the correlation between thiocyanate space and surface area was 0.94, it is difficult to see why thiocyanate space is a more useful index of "metabolic size" than is surface area.

VOL. 2 1955

containing 0.025 Gm. Evans Blue, 1.396 Gm. sodium thiocyanate, and 1.0 Gm. antipyrine. Blood samples were drawn at 2,3,5, and 7 hours after the injection for appropriate spectrophotometric measurements.[40,51] All determinations were made under basal conditions except for a light fat-free breakfast which was permitted one hour prior to the beginning of the body water estimates. Basal metabolism was determined by the Tissot open circuit method on each of two different days.[53]

The average plasma volumes and thiocyanate spaces did not change significantly with age, but the antipyrine space decreased both absolutely and in relation to body weight or surface area. Thus it is probable that most of the decrement in total body water represented a loss in the intracellular component. Since the water content of cellular protoplasm does not apparently change significantly with age, a reduction in the intracellular water phase of the entire body indicates a loss in active protoplasm.

The results are summarized in Fig. 3. The previously described reduction in basal heat production per square meter of surface area, with increasing age, is shown by the solid line connecting the open circles. The dotted line connecting the open circles illustrates the total body water, per square meter of surface, which also diminishes with age. When the average oxygen uptake per liter of body water (calculated for each individual subject) is plotted, no change with age occurs (solid line connecting solid circles). If total body water is accepted as an index of the amount of functioning protoplasm in the individual, these observations are not in accord with the hypothesis that the metabolic rate of cells diminish with age, at least in the male.

Tissue Metabolism.—Examination of the literature on age changes in resting oxygen uptake of cells and tissues in vitro ought to give additional information on the question of whether cellular metabolism diminishes with age. However, even these studies are confronted with the previously encountered problem of determining the amount of functioning protoplasm present in the tissues. For the most part, determinations of the nitrogen content or dry weight have been used. Neither of these measures give the basic information required; namely, the number of cells or the amount of functioning protoplasm in the preparation.

Although many investigators have measured the resting oxygen uptake of tissues and cells under a variety of circumstances, very few have included aged animals in their studies. Pearce[54] reported a 38 per cent decrease in oxygen uptake of liver slices and a 11.5 per cent decrease in kidney slices from mice between the ages of 4-9 weeks and 50-60 weeks.* These calculations were based on wet weight and cannot be interpreted as a decrement in cellular metabolism. Ross and Ely[57] have reported a decrement in endogenous oxygen uptake in liver slices from young (4 weeks) and old (21 months) rats. The decrement remained even when the oxygen uptakes were corrected to dry weights. In contrast, Hawkins[58] found no age changes in (1- to 2-year-old animals) the resting oxygen uptake, based on dry weight, of liver slices from the rat. Wollenberger and

*Mortality data for both rats and mice indicate a 50 per cent survival rate from birth to 24 months.[55,56]

Jehl[59] found no difference in oxygen uptake per unit of dry weight in heart tissue from guinea pigs between the ages of 6 months and 6 years.

Other investigators have utilized tissue homogenates for the determination of oxygen uptake of tissues. Rafsky, Newman, and Horonick[60] examined kidney and liver homogenates from guinea pigs aged 8 weeks to 2 years. Since 7-year-old guinea pigs have been reported, it seems unlikely that a 2-year-old animal is really aged. Within the age groups studied, Rafsky found no significant changes in the oxygen uptake, per milligram tissue nitrogen or original weight, in the liver, but did find a decrease of approximately 60 per cent in kidney. Reiner[61] studied homogenates of liver and brain in 6-month-old and 2-year-old rats. His data showed a significant drop in oxygen uptake per milligram dry weight for both liver and brain in the old animals.

It is impossible to come to any clear conclusions on the basis of the data available in the literature since the number of animals used is always small, there are marked discrepancies in the data, different species have been used, and the problem of determining cell number has not been faced.

VOL. 2 1955

TABLE IV. RESTING OXYGEN UPTAKE OF BOVINE ARTICULAR CARTILAGE
(From Rosenthal, Bowie, and Wagoner: J. Cell. Comp. Physiol. 17:221-223, 1941)

AGE SPAN (YR.)	NUMBER OF CELLS PER MM^3 FIXED TISSUES		TOTAL O_2 UPTAKE MICROLITERS PER HOUR PER MG. DRY WT.				O_2 UPTAKE PER NUCLEUS MICROLITERS PER NUCLEUS PER HOUR	
	N	$\times 10^3$	N	RESTING MG. WT. WGT.	N	ANAEROBIC GLUCOLYSIS MG. WT. WGT.	RESTING	ANAEROBIC GLUCOLYSIS
Less than 0.5	4	133	12	.088 ± 0.0017	9	1.21 ± 0.101	0.66	0.845
1– 7	3	47.2	30	.024 ± 0.010	12	0.438 ± 0.089	0.51	0.925
8–11	11	34.0	11	.008 ± 0.005	12	9.259 ± 0.059	0.24	0.764

In only one age-wise study has the oxygen uptake of the tissue been related to the actual number of cells. Rosenthal, Bowie, and Wagoner[62,63] determined manometrically the resting oxygen uptake and the anaerobic glucolysis of slices of bovine articular cartilage as well as the number of cells per cubic millimeter of the tissue. Table IV summarizes the pertinent data from their paper. Although the number of animals tested is small, significant decreases in the number of cells, the endogenous oxygen uptake, and the rate of anaerobic glucolysis were observed. However, the anaerobic glucolysis of the tissue was highly correlated with the number of nuclei identified histologically ($r = 0.956$) so that the glucolysis rate, per nucleus, did not change significantly with age. On the other hand, the endogenous oxygen uptake did diminish significantly with age. This is the only study, thus far, presenting evidence of a diminution in the metabolic activity of cells with increasing age. Cartilage is a slowly metabolizing tissue which may or may not be representative of other tissues in the body. Certainly it makes only a small contribution to the total oxygen uptake of the intact individual.

At the present time, no definite conclusion can be reached about age changes in cellular metabolism on the basis of observations on tissues. Additional studies are required, utilizing animals of known genetic[64] and nutritional histories.[65] A number of indices of the amount of functional protoplasm should be applied simultaneously to a variety of organs and tissues in the same animal. In addition to dry weight and nitrogen content, chemical determinations of nuclear components as well as actual nuclear counts should be explored as indices of functional protoplasm.

Age Changes in Cellular Response to Thyroid Hormone.—This is a question for which we have no clear-cut data. It is true that some clinicians have noted an increase in basal metabolism in older subjects following the administration of small amounts of thyroid hormone. Thus, Binet and Bourlière[29] report a single case where the basal metabolism was increased from 22.5 to 31.6 cal./sq. M./hr. following the daily administration of 100 mg. dessicated thyroid over a period of two months. Similarly, Kountz and Chieffi[34] have been impressed by the increase in BMR following the clinical use of thyroid substance. Unfortunately for the experimental design, the therapy also included androgens, estrogens, iodine, and amino acids, so that the response to thyroid substance in their patients was not established. Up to the present, no careful evaluation of age differences in the response to standardized amounts of thyroid hormone has been reported.

It would be possible to study this problem in animals by measuring the tissue oxygen uptake in animals of different ages which have been given known amounts of thyroid substance, but, at the moment, these data are lacking. The question of age differences in tissue response to thyroid hormone cannot be investigated with tissue slices, since no effect on oxygen uptake can be detected.[66]

Adequacy of Supply of Thyroid Hormones.—If the metabolism of the cells in the aged subject is reduced, it might be due to inadequacy of the thyroid gland to supply the usual amount of hormone. Structurally, the thyroid gland changes with age. In subjects 60 to 80 years of age, the gland is reduced in size, the follicles and cells are smaller, the colloid content is diminished or absent, and much less mitosis is seen in the epithelial cells.[67-70] Although many have interpreted these changes as evidence of primary hypothyroidism in advanced age, we have no real basis for this assumption. In view of the large factors of safety in normal thyroid glands, it is possible that, even in the glands described, adequate supplies of hormone were being released. We do not know how far reduction in gross size of the gland, or reduction in size and number of epithelial cells, can go before the output of thyroid hormone falls below a level adequate to maintain metabolism.

The level of protein-bound iodine in the blood is often used as an index of thyroid function.[71] The evidence for an age change in PBI is scanty and uncertain. Kountz, Chieffi, and Kirk[20] reported a gradual decline in the average values for men between the ages of 25 and 80, but no change in women. In the men, the value was 5.7 μg per 100 c.c., at age 40 to 59, 4.2 at 70 to 79, and

3.3 above 80. Since the standard deviations were high (2.6 to 1.3), there is considerable overlapping of measurements in successive decades even for the men. The authors concluded that their findings "support the assumption of a decreased thyroid function in the men with age." Other investigators, such as Starr and his associates[71,72] and Perlmutter and Riggs[73] have failed to find any significant change in the PBI with increasing age.*

Tucker and Keys[76] compared the PBI in 130 young men (age 18 to 25) with 272 middle-aged men (age 45 to 56). Although the mean value for the middle-aged (5.63 μg per 100 c.c.) was significantly lower than that of the young men (6.24 μg per 100 c.c.), the range of values was practically the same for both groups. The difference was due largely to the skewed distribution in the middle-aged groups. The correlation between BMR and PBI in the total group was low (+0.113, significantly greater than zero) but was insignificant in either age group separately. Thus, for the normal men studied, variations in basal oxygen consumption were associated with factors other than levels of PBI circulating in the plasma. One may, therefore, question the usefulness of the plasma PBI determined by methods now available as an index of thyroid function within the normal range.†

VOL. 2 1955

TABLE V. AGE AND AVERAGE 24-HOUR ACCUMULATION OF I^{131} IN EUTHYROID SUBJECTS

(Data recalculated from Quimby, Werner, and Schmidt: Proc. Soc. Exper. Biol. & Med. 75:537-540, 1950)

AGE (YEARS)	PER CENT OF AMOUNT OF I^{131} ADMINISTERED								
	MEN			WOMEN			TOTAL		
	N	MEAN	σMN.	N	MEAN	σMN.	N	MEAN	σMN.
<20	17	27.1	2.3	32	27.4	2.0	49	27.3	1.43
20–29	30	26.6	1.2	165	27.0	0.6	195	26.9	0.53
30–39	42	24.3	1.3	186	26.5	0.6	228	26.1	0.55
40–49	73	22.9	0.9	118	25.7	0.8	191	24.6	0.61
50–59	66	22.8	0.8	84	24.5	1.1	150	23.7	0.71
60–69	34	21.4	1.2	54	22.6	1.2	88	22.1	0.85
70–86	22	22.8	1.7	29	23.5	2.0	51	23.2	1.28

The accumulation of radioactive iodine by the thyroid gland has proved a useful clinical test for thyroid dysfunction. Although no specific studies of age changes in I^{131} uptake of the thyroid gland have been made, Quimby, Werner, and Schmidt[78] have analyzed hospital data on an age basis. Measurements of 24-hour uptake, by counting over the gland following oral administration of

*Klein[74] and Bürger[75] have reported a significant increase in total blood iodine content with increasing age (from 18.2 at age 20 to 28.4 μg per 100 c.c. at ages over 80). The authors interpret their results as an indication of reduced ability of the thyroid gland to take up the inorganic iodine from the circulatory blood. More direct investigations of this question, using I^{131}, do not lend support to this interpretation.

†This, of course, does not deny the clinical usefulness of the PBI for diagnostic purposes, since the inclusion of hypo- and hyperthyroid subjects in a total distribution will result in a high correlation between PBI and BMR.[77]

I^{131}, showed a gradual but small decrement between the ages of 20 and 80 years (Table V). Although the age trend is statistically significant, the investigators regarded it as of questionable clinical importance. The small decrement with age might be a reflection of the diminution in the amount of active thyroid tissue itself rather than an index of impaired function. Since the test would be done primarily in subjects with some clinical indications of metabolic disturbances, it is scarcely proper to utilize these clinical observations as an index of age changes, even though patients with detectable thyroid disease were subsequently removed from the group.

A more pertinent index of age changes in the functional capacity of the thyroid gland might be offered by estimates of the rate of uptake of iodine, since differences in rates might be missed by measurements of uptake taken after 24 hours. There is some evidence that this might be the case in a small series of subjects tested by Perlmutter and Riggs.[73] In this study, estimates of the "accumulation gradient" of radioactive iodine in the thyroid gland were made by estimating the slope of the plot of counts per minute against $\sqrt{t}$, where t was 1, 2, 3, and 4 hours after oral administration of NaI^{131}. The average values show a progressive fall with age (Table VI). If the data for males are divided into two groups, age 20-50 and 50-80, there is a statistically significant difference in the accumulation gradients. In view of the small number of subjects studied, the marked difference in the accumulation gradients found in males and females over 70 years of age, and the uncertainties of oral administration, this study needs confirmation.

TABLE VI. AGE AND ACCUMULATION GRADIENTS OF I^{131}
(Data from Perlmutter and Riggs: J. Clin. Endocrinol. 9:430-439, 1949)

AGE	MEN		WOMEN	
	N	MN. $\pm$ 1 SD_{MN}	N	MN. $\pm$ 1 SD_{MN}
12–19	11	4.4 $\pm$ 0.95	6	4.1 $\pm$ 0.62
20–29	13	3.8 $\pm$ 0.53	13	4.7 $\pm$ 0.65
30–39	7	2.8 $\pm$ 0.08	10	4.4 $\pm$ 0.95
40–49	14	2.9 $\pm$ 0.71	12	5.4 $\pm$ 0.95
50–59	12	2.0 $\pm$ 0.31	20	2.5 $\pm$ 0.42
60–70	11	1.8 $\pm$ 0.25	20	2.2 $\pm$ 0.33
70+	4	0.6 $\pm$ 0.20	9	2.4 $\pm$ 0.38
20–49	34	3.2 $\pm$ 0.36	35	4.8 $\pm$ 0.47
50+	27	1.7 $\pm$ 0.19	49	2.4 $\pm$ 0.22
Diff. of Mn.		1.5 $\pm$ 0.43		2.4 $\pm$ 0.51
t		3.5		4.6

Ackermann and Iversen[79] have measured the radioiodine excretion over a 72-hour period after oral administration of a tracer dose in 24 male and 25 female subjects, all 60 years of age or older, without evidence of thyroid or renal disease. Although the values observed were lower than those reported by other investigators for young adults, no significant changes were noted in either the

renal excretion rate or the calculated thyroid uptake rate. In view of the known reduction in renal function with age,[80,81] it is difficult to interpret data based on urinary values alone. Since the authors made no tests on young controls, it cannot be said that their data demonstrate an age difference in the rate of uptake of I^{131} by the thyroid.

In summary, we can only conclude that clear-cut evidence for a reduction in the functional capacity of the thyroid gland in old age is still lacking. The data are either negative, as for example changes in PBI, or controversial, as are the data on rate of uptake of radioactive iodine.

Reduced Stimulation of the Thyroid.—In view of the role of the pituitary in controlling the level of activity of the thyroid gland, it is necessary to consider the possibility of age changes in the secretion of thyroid stimulating hormone (TSH) as a source of reduced metabolism in older people. Although a number of studies have shown that administration of TSH will increase the rate of uptake of I^{131} by the thyroid, increase the amount of circulating PBI, and stimulate metabolism,[82,83] no studies on age differences in these responses have been reported. With the recent availability of improved preparations of TSH, these studies may now be made in man.

VOL. 2 1955

SUMMARY

In summary, it may be said that basal oxygen consumption of the total person diminishes gradually with increasing age. This decrement remains even when the determinations are corrected for differences in body size, based on estimates of surface area. In all probability, the basal metabolism per unit of surface area of females remains below that of males even at advanced ages. However, when calculations of basal oxygen consumption are based on the total body water content of the individual, age trends disappear, at least in males. Presumably this means that the reduction in metabolism, with age, is more the result of loss of body tissues and cells having relatively high oxygen consumption rates than it is a reflection of reduced metabolic activity of the cells remaining. Data on resting oxygen uptake of tissue slices offers little evidence for a decrease in oxygen uptake per cell nucleus, with the exception of bovine articular cartilage. Nor is there good evidence of impaired thyroid function in elderly people. Although there may be a slight reduction in the 24-hour uptake of I^{131} in aged people, the best evidence of reduced thyroid function is based on a small sample which showed a significant reduction in the accumulation gradient of I^{131} in the thyroid of subjects over 70. Thus, it cannot be assumed that the rate of cellular metabolism necessarily diminishes with increasing age. With the development of new techniques, which may permit identification of active principles from the thyroid in the circulating blood and tissues, it should be possible to resolve some of these important problems.

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VOL. 2 1955

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OL.
2
955

Book Reviews

ENDEMIC GOITER: THE ADAPTATION OF MAN TO IODINE DEFICIENCY. By John B. Stanbury, M.D., Gordon L. Brownell, Ph.D., Douglas S. Riggs, M.D., Hector Perinetti, M.D., Juan Itoiz, Ph.D., and Enrique B. Del Castillo, M.D. Pp. 206, with 53 figures, indexed. Cambridge, Mass., 1954, Harvard University Press. Price $4.00

Endemic goiter due to iodine deficiency is now rarely observed. The disorder received worldwide attention and study in the period between the two World Wars and has been generally eradicated by the judicious addition of iodide to table salt. The availability of radioiodine following the second World War in association with the development of radioisotope techniques presented a method for new studies in endemic goiter. The opportunity to make such studies was clearly recognized by Dr. James Howard Means, Dr. John B. Stanbury, and their associates at Harvard, when the Argentine physician, Dr. Perinetti, brought news of an area of endemic goiter in Mendoza. Stanbury, along with two of his colleagues, Brownell and Riggs, joined hands with Perinetti and two other Argentines, Itoiz and Del Castillo, to apply their isotopic experiments to goitrous subjects.

Much of the book is devoted to the higher mathematics necessary to derive conclusions regarding the experimentation. Although these chapters might prove tedious to some, other sections make easy and delightful reading.

These studies showed that the thyroid gland of a goitrous individual was extremely avid for iodine, and that it manufactured and released thyroid hormone rapidly. Although overt myxedema was infrequently encountered, the lower the serum concentration of thyroid hormone (as measured by protein-bound iodine in serum) the greater were the rates of thyroidal radioiodine accumulation, conversion to hormone, and secretion into the general circulation. The kidney appeared not to have mechanisms for the conservation of iodide when dietary intake was low. Also of interest was the observation that one goitrous patient became thyrotoxic when given 1.5 mg. of iodide daily.

This work expands the classic studies of Marine on endemic goiter and in itself is a masterful study.

Samuel P. Asper, Jr.

ATLAS DER HAUT—UND GESCHLECHTSKRANKHEITEN. By Prof. Dr. W. Frieboes, and Prof. Dr. W. Schoenfeld. Pp. 292; indexed. Stuttgart, Germany, 1955, Georg Thieme. Price $28.10.

The second edition of this fine work contains 390 colored illustrations (autochrome method), 69 in black and white, 14 dermatograms, 2 microphotographs, and 1 roentgenogram. They were collected by the late Walter Frieboes and by Walther Schoenfeld in Heidelberg. Though they had to be selected according to the material available, and according to their importance to the German physician and dermatologist, they give a good cross section of dermatologic pictures seen by the physician in other countries. Usually clear-cut clinical pictures are chosen, but aberrant forms and rare conditions are also well represented. Skin manifestations incidental to internal diseases are amply covered.

Of particular interest are the dermatograms. Schoenfeld has modified the technique of Kromayer (1896) (similar to today's fingerprinting) and copies the prints onto light sensitive paper. These positive prints yield a better and more plastic picture of the relief of the skin which is quite typical in a number of dermatoses, such as acanthosis nigricans, Darier's disease, striae, and others.

VOL. 2 1955

The deep mycoses are not represented. This is well compensated for by the wealth and excellency of material in the chapters on tuberculosis of the skin (28 illustrations) and syphilis (62), which alone are worth the price of the atlas to the American physician and teacher. Numerous and most unusual late manifestations of these two chronic diseases are shown, such as the middle-aged dermatologist of today has hardly ever seen, nor is likely to see in the future. These pictures, which the author hesitated to include on account of their rarity in today's practice, make the atlas also a historical document of value.

The diagnoses to most pictures are given in Latin. On the facing pages the legends are sometimes amplified in the form of short case histories. Most diseases are discussed as to etiology, clinical appearance, diagnostic features, and treatment. While necessarily brief they are sufficient to familiarize the physician with the present-day views of German dermatologists. The treatment suggested differs occasionally from the methods used in the United States.

Unfortunately, many medications are listed only by their proprietary names, unknown in some instances outside of Germany. The value of the book would be enhanced if the publisher would add, to the copies going abroad, a loose sheet with a glossary giving the chemical names of all proprietary medications discussed in this truly great atlas.

John A. Gammel

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Books Received

RUTIN AND RELATED FLAVONOIDS. By John Q. Griffith, Jr., M.D., John Q. Griffith, Charles F. Krewson, Ph.D., and Joseph Naghski, Ph.D. Easton, Pennsylvania, 1955, Mack Publishing Company. Price $7.50.

ANNALS, Vol. 59, Art. 2, "PAUL EHRLICH CENTENNIAL." By R. J. Schnitzer and other Pp. 136. New York City, 1954, The New York Academy of Sciences. Price $3.00.

J.A.M.A. CLINICAL ABSTRACTS OF DIAGNOSIS AND TREATMENT. Edited by Noah D. Fabricant. Pp. 627; indexed. New York City, 1955, Intercontinental Medical Book Corp. and Grune & Stratton, Inc. Price $5.50.

VOL.
2
1955